

A Pilot Study to Test Multiple Medication Usage And Driving Functioning

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16. Abstract

The use of medications and multiple medications becomes more prevalent with increasing age. This pilot study explored the relationship between polypharmacy and driving functioning through separate but related research activities. A patient-level administrative claims database containing prescription information as well as E-codes identifying the incidence of motor vehicle injuries was mined, yielding combinations of drugs that became inclusion criteria in a following field study of driver performance among 44 older adults (range: 57 to 89; mean: 79). Driving performance evaluations by an OT/CDRS, a brake response time measure, and functional screening measures were conducted for the study sample, whose drug profiles were documented through a "brown bag" review by a licensed pharmacist. The relationship between medication usage and each of these outcome measures was examined in descriptive data summaries and regression analyses. The driving evaluations were carried out in a dual-brake vehicle also equipped with speed sensor (OBD-2), GPS logger, and two miniature video cameras (driver's face and forward road views) plus digital recorder. A subsample allowed the same instrumentation package to be installed in their private cars for a week of independent driving; this supported an analysis of within-subject variability in driving behavior during a formal driving evaluation versus independent driving.

Additional project activities included a current (to October 2007) review of the literature on the prevalence of prescription medications and effects on driving of specific drugs/drug classes. The feasibility of conducting future studies using large, administrative claims databases was critically examined, with an overview of candidates and evaluation of their suitability for NHTSA research. This report concludes with a discussion of project findings and recommendations for future research.

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LIST OF ACRONYMS AND ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ADR	Adverse Drug Reaction
AHRQ	Agency for Healthcare Research and Quality
ARCI	Addiction Research Center Inventory
ASF	Advanced Systems Format
BRT	Brake Reaction Time
CAPI	Computer-Assisted Personal Interviewing
CCRC	Continuing Care Retirement Center
CERTs	Centers for Education and Research on Therapeutics
CDRS	Certified Driver Rehabilitation Specialist
CMS	Centers for Medicare & Medicaid Services
CNS	Central Nervous System
COX	Cyclooxygenase
CRO	Controlled-Release Oxycodone
CSH	Carotid Sinus Hypersensitivity
CVS	Cardiovascular System
d.f.	Degrees of Freedom
DC	Direct Current
DHI	DrivingHealth® Inventory
DSS	Decision Support System
DSST	Digit Symbol Substitution Test
DUA	Data Use Agreement
EEG	Electroencephalogram
FARS	Fatality Analysis Reporting System
FRIDS	Fall-Risk-Increasing Drugs
GPRD	General Practice Research Database
GPS	Global Positioning System
HCUP	Healthcare Cost and Utilization Project
HIPAA	Health Insurance Portability and Accountability Act
HMG/COA	5-Hydroxy-3-Methylglutaryl-Coenzyme A
HMO	Health Maintenance Organization
Hz	Hertz
IRB	Institutional Review Board
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
KML	Keyhole Markup Language
LCD	Liquid Crystal Display
MAX	Medicaid Analytic eXtract
MCBS	Medicare Current Beneficiary Survey
MHRA	Medicines & Healthcare Products Regulatory Agency
MSIS	Medicaid Statistical Information System
MSS	Musculoskeletal System
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NDC	National Drug Code
NHS	National Health Service

LIST OF ACRONYMS AND ABBREVIATIONS (Cont'd)

NHTSA	National Highway Traffic Safety Administration
NIS	Nationwide Inpatient Sample
NMEA	National Marine Electronics Association
NRAR	Norwegian Road Accident Registry
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OBD	On-Board Diagnostic
OCME	Office of the Chief Medical Examiner
OH	Orthostatic Hypotension
OR	Odds Ratio
OT	Occupational Therapist
OTC	Over the Counter
PBM	Pharmacy Benefits Management
PDI	Potentially Driver Impairing
PI	Principal Investigator
PIP	Potentially Inappropriate Prescription
RT	Reaction Time
Rx	Prescription
SDLP	Standard Deviation of Lateral Positioning
SIR	Standardized Incidence Ratio
SMRFs	State Medicaid Research Files
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSN	Social Security Number
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TOVA	Test of Variables of Attention
TRB	Transportation Research Board
VHA	Veteran's Health Administration
VVC	Vasovagal Collapse
X^2	Chi-Square Test Statistic

EXECUTIVE SUMMARY

The number of older licensed drivers in the United States is growing at a rate faster than the overall population. As people age, they are more likely to take one or more potentially driver-impairing (PDI) medications. TransAnalytics, LLC, completed a pilot study to gain a better understanding of the safety impact on older drivers of taking multiple PDI medications, providing an update on the prevalence of prescription medications in the older population, and the effects on driving of specific drugs/drug classes. Research activities included a literature review; a data mining exercise; the prioritization of other databases for future data mining; and a field study including on-road evaluations of older drivers who take multiple PDI medications by an occupational therapist, and associated instrumented vehicle observations. The results of this work point to what appear to be relatively stronger, and weaker, strategies for carrying out future studies in this vital area of research.

The literature review in this project examined recently published research to update a prior NHTSA report (Literature Review of Polypharmacy and Older Drivers: Identifying Strategies to Study Drug Usage and Driving Functioning Among Older Drivers, DOT HS 810 558) on the effects of different types of PDI drugs on driving. New information about specific drugs/drug classes and driving is provided for an anti-seizure medication (topiramate) used for migraine prevention and other therapies; acute and stable dosing of opioids; sedating and non-sedating antihistamines; antidepressants; short- and long-half-life sedative-hypnotics; an immediate-release versus extended-release anti-anxiety medication (benzodiazepine); a skeletal muscle relaxant (carisoprodol); and anti-diabetic medications. In addition, this review provided insight into the risk associated with chronic medical conditions versus the effects of the medications that treat these conditions.

This question was examined in the context of studies bearing on the risk of falls; there is evidence that the same medications that mediate falls risk may also mediate motor vehicle crash risk. What emerges in this review is that some geriatric patients experience an increased risk of falling due to cardiovascular adverse effects of sedatives, antihypertensives, and other medications, and that when these fall-risk-increasing drugs are withdrawn there is a resulting, persistent benefit — a significant reduction in the occurrence of falls (Van der Velde et al., 2007). At the same time, researchers have found that chronic medical conditions were often more important than medications in causing falls in high-functioning community-dwelling older people (Lee et al., 2006). This underscores a need for NHTSA to sponsor future, periodic updates to remain current with new research. Also, many older people are likely to benefit from an individualized medication review by their pharmacist, with physician follow-up, potentially leading to the withdrawal of selected medications, for selected conditions, and/or their replacement with alternative prescriptions without known PDI (or fall-risk-increasing) effects.

This project defined an ideal database to study the crash involvement of older drivers taking PDI medications— which would contain linked medical, hospital, and pharmaceutical data for each eligible person and would be the *only* provider of services—then evaluated a number of candidates for such work. The “ideal” database, which would capture the complete record of drug utilization for a patient (driver), unfortunately does not presently exist. However, several promising candidates for future NHTSA investigations were identified, in particular, the

Ingenix LabRx® database (United Healthcare) and the Veteran's Health Administration Pharmacy Benefits Management Database (VHA/PBM).

In this project, data mining was performed in the Pharmetrics database, a patient-level administrative claims database containing prescription information and E-codes signifying the incidence of motor vehicle injuries to identify drivers who were taking PDI medications and were involved in crashes. The number of PDI drugs taken by crash-involved individuals within the age cohorts from 16 through 49, and within 5-year cohorts from 50 up through 75+, ranged from zero to 16. The use of multiple PDI medications by crash-involved drivers, who are 50 and older, climbs steadily with age, until leveling off at the 65- to 69-year-old cohort. At the same time, one-third to one-half of crash-involved drivers in each of these cohorts were taking no PDI medications. From this exercise, a set of two PDI drug combinations—hypotensives in combination with one or more other classes of PDI medications such as lipotropics, beta blockers, calcium channel blockers, NSAIDS, SSRIs, and gastric acid secretion reducers—emerged as inclusion criteria for a subsequent field study.

Forty-four healthy older drivers between the ages of 57 and 89, who drove 50 miles and/or three days each week, participated in a pilot study to examine their use of PDI medications and driving abilities. A pharmacist collected data on each participant's medication usage via one-on-one "brown bag" medication reviews. Each driver's functional status was measured using a computer-based test battery including high- and low-contrast acuity measures, plus physical and cognitive measures validated as significant predictors of at-fault crashes among seniors in earlier NHTSA research. Then, an occupational therapist/certified driver rehabilitation specialist (OT/CDRS) measured drivers' on-road performance. This included onboard measures of brake response time under alerted and un-alerted conditions.

Due to the small sample size relative to the number of drugs and drug classes, logistic regression was unable to significantly associate medication usage with observed differences in functional (cognitive) status, driving evaluation outcomes, or brake response time. It was observed that the drivers who "failed" the OT evaluation were also among the oldest, however. This may be an indication of greater impairment in driving performance due to PDI medications with increasing age, due to a wide range of physiological changes and changes in how these drugs are metabolized. While these results must be regarded as tentative, it appears that ACE inhibitors, generally, and ACE inhibitor/thiazide diuretic combinations may deserve special attention in future research.

The private cars of a sub-sample of 5 individuals who underwent evaluation by the OT/CDRS were equipped with instruments to collect video, GPS and speed recordings, as they drove independently. These same instruments were present during their drives with the OT, which took place on the same roads, at similar times of day and under similar conditions. The goal was to examine the variability in behaviors serving as surrogates of driver attention/ distraction, plus speed choice, as a function of driving context. In the aggregate, these drivers spent more time looking down and inside the vehicle and less looking toward the inside rearview mirror when driving independently than when the OT was present, including during intersection negotiation. A case study also revealed that, on common road segments, an 82-year-old study participant was more likely to drive slower on her own than during the OT evaluation, when

other traffic was present; but *faster* on her own under "empty road" conditions, where other traffic could not affect speed choice. Such differences between independent driving and (older) peoples' behavior during a driving evaluation may have significant safety implications.

One important conclusion from this pilot study is that small-sample empirical investigations do not appear to be a practical route to a better understanding of (multiple) medications and driving impairment. The prevalence of PDI drugs in any population-based sample works against successfully modeling the predictor-criterion relationships of greatest interest; and, sample recruitment is daunting. At the same time, two promising methods for future research can be recommended. First, databases highlighted in this report can be used to mine patient-level information, an approach that may be quite valuable in pinpointing drugs and combinations of drugs to target in future information and education interventions. Further, there is preliminary evidence to recommend monitoring (with consent) drivers' behavior using unobtrusive, affordable, miniature in-car instrumentation packages. This research methodology offers a unique opportunity to measure behavioral variability as a function of driving context, and to determine normative exposure levels to a wide range of hypothesized risk factors.

INTRODUCTION

PROJECT OBJECTIVES

This project sought to identify trends in exposure to potentially driver impairing (PDI) medications by seniors and then, using complementary approaches, to improve our understanding about how the use of multiple medications relates to the ability to drive safely. These goals were accomplished by satisfying the following specific objectives:

- Critically review new reports, surveys, and other studies throughout the entire project to continuously update the state-of-the-knowledge concerning older adults who are at risk from exposure to PDI medications.
- Use a proprietary, patient-level database supplied by NHTSA to perform data mining to better characterize drug use among older adults, and in particular, to identify subgroups of drugs and combinations of drugs that are most strongly associated with injurious motor vehicle crashes.
- Design and conduct a pilot study using field data collection procedures to reveal how specific combinations of prescription and over-the-counter medications effect driving behavior under defined observational conditions, using both between- and within-subjects analysis methods.
- Evaluate the feasibility of using large, administrative claims databases to conduct further NHTSA research investigating driver characteristics, medication usage, and crash and injury experience.
- Develop recommendations for a research strategy that is most likely to result in findings that will support future NHTSA efforts to inform individuals, and their pharmacists, physicians and other health care providers, about the impact of medication usage on safe driving.

BACKGROUND

The number of older, licensed drivers in the United States is growing at a rate faster than the overall population. In 1988, at the time the first TRB Special Report *Transportation in an Aging Society* was published, 12% of the population was 65 or older. By the year 2020, the U.S. Census Bureau projects that roughly 1 in 5 people will be 65 or older, and almost half of those will be 75 or older. At the same time, reliance on the private automobile as the primary means of transportation, either as a driver or passenger, is increasing for this segment of the population. The increasing frailty that comes with advancing age means that older vehicle occupants, if involved in a crash, will suffer more serious injuries and are at significantly greater risk of being killed than their younger counterparts. In 2001-2002, per mile driven, drivers 80 and older had higher rates of passenger vehicle fatal crash involvements than drivers in all other age groups except teenagers, and those 85 and older had the highest rates (Insurance Institute for Highway Safety, 2003). When the driver fatality rate is calculated based on the estimated annual travel, the rate for drivers 85 and older is *ten times highe*r than the rate for drivers age 30 to 60.

There are a number of factors that may contribute to the increased crash and fatality rates among older drivers, most notably a range of age-related diminished capabilities documented in related NHTSA projects (Staplin, Gish, and Wagner, 2003). At the same time, the medical conditions that are more prevalent in old age and the medications used to treat them have come under increased scrutiny as the reason for such declines.

In 2004, 37.4% of non-institutionalized people over 65 assessed their heath as excellent or very good; this compared to 65.8% for people 18 to 64 (Administration on Aging, 2004). Most older people have at least one chronic condition and many have multiple conditions. Among the most frequently occurring conditions among older people in 2000-2001 were: hypertension (49.2%), arthritic symptoms (36.1%), all types of heart disease (31.1%), any cancer (20.0), sinusitis (15.1%), and diabetes (15.0).

In a cohort study of nearly 28,000 Medicare+Choice enrollees cared for by a multi-specialty practice (an ambulatory clinic setting) during a 12-month study period between 1999 and 2000, researchers found that 75% of the sample received prescriptions for six or more prescription drugs (Gurwitz, Field, Harrold, Rothchild, Debellis, Seger, Cadoret, Fish, Garber, Kelleher, & Bates, 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. 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%)

Hébert, Bravo, Korner-Bitensky, and Boyer (1996) found that the consumption of three or more drugs per day increases the risk of functional decline in elderly people by 60% (cited in Allard, Hébert, Rioux, Asselin, & Voyer, 2001). In a recent and comprehensive National survey of U.S. noninstitutionalized adults, Gurwitz (2004) reported that more than 90% of people 65 or older use at least 1 medication per week; more than 40% of this population uses 5 or more different medications per week; and 12% use 10 or more different medications per week. The risks of polypharmacy include an increase in the number of potentially inappropriate

prescriptions, cognitive disorders, falls, hip fractures, depression, and incontinence (Gurwitz, Soumerari, & Avorn, 1990). Additionally, the results of a recent NHTSA study have suggested that there is an increased risk of motor vehicle crashes for older drivers who use multiple potentially driver-impairing medications (LeRoy & Morse, 2005).

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 (central nervous system) 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, Beers, Steiner, Aronow, Rubenstein, and Beck (1994) who found that depressed, community-dwelling elderly were eight times as likely as their non-depressed counterparts to be prescribed a long-acting benzodiazepine in addition to their antidepressant medication.

In theory, all psychoactive compounds (depending on dose), may have detrimental effects on psychomotor performance underlying driving skills (Walsh, de Gier, Christopherson, & Verstraete, 2004). 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 Leroy and Morse's (2005) 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 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 + 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;
- Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants + Narcotics;
- Narcotics + NSAIDs + Antibiotics.

Preliminary results of Leroy and Morse's (2005) analysis indicate that 64% of the drivers 50 and older who had a motor vehicle crash had received a prescription for a potentially driver-impairing medication within the prior 60 days. This compares to 54% 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, anti-diabetic agents, anti-anxiety agents, antihypertensive agents, and skeletal muscle relaxants.

Together, these facts—much higher numbers of older people in the population, who rely to an overwhelming extent on automobiles, are at exaggerated risk of death or injury in a crash, experience age-related diminished capabilities and medical conditions that affect safe driving performance, and take multiple medicines that alone or in combination are potentially driver impairing—lend urgency to continuing investigations to identify medication use in this population and to determine the effects of (multiple) medications on driving functioning.

Data Mining of Administrative Database

Data Mining Objective

The goal in this project task was to conduct exploratory analyses in a proprietary database that is the property of NHTSA, the PharMetrics Patient-Level Database developed through a prior contract (LeRoy & Morse, 2005), to identify trends in the usage of medications within subgroups of older drivers that could help guide the research design for the present project. In particular, we were seeking to update and refine our understanding about the exposure of seniors to potentially driver-impairing prescription medications, and to prioritize specific combinations of PDI medications for the later pilot study. The database analyses described herein were performed mainly by the Highway Safety Research Center at the University of North Carolina.

The PharMetrics database consists of SAS tables summarizing information about individuals with (cases) and without (controls) motor vehicle crash involvement, who are enrolled in prescription medication insurance plans. It includes ICD-9-CM classification codes for causes of injury ("E-codes") together with entries for patient demographics, number of medications dispensed, patterns of medication combinations, and disease prevalence, for 33,519 "cases" (patients with crashes in the enrollment population) and for 100,557 "controls" (patients without motor vehicle crashes in the enrollment population). A subset of 22,574 cases was selected for the present analyses, as described below. Also, the database includes records for crash-involved drivers only if (1) the driver sustained an injury severe enough to result in a hospital treatment and associated insurance payment, and (2) the driver had at least 6 months of continuous insurance coverage prior to the date of the crash/injury. For these reasons, this dataset may not be truly representative of the (older) American population, i.e., biases from these selection factors are certainly plausible. It also may be noted that there is no indication of "fault" for the crashes encompassed in this database.

Analyses reported by LeRoy and Morse provided the starting point for the present work. These researchers examined occurrences of drug-drug conflicts and drug-disease conflicts in the database, performing odds ratio calculations on cases versus controls. The drug classes for which statistically significant relationships were demonstrated are presented in Appendix VIII, Table 1 of their final report; these relationships were used as a selection factor in the present analyses.

METHODS AND RESULTS

The selected cases included in the database developed by LeRoy and Morse (2005) reflect subsets of E-codes that exclude, for example, collisions with trains; injuries suffered when boarding or alighting from a vehicle (e.g., a bus); and other non-collision-related injuries that are associated with motor vehicle use (e.g., poisoning from exhaust fumes). Crash types included in the database are: E811—*motor vehicle traffic accidents involving re-entrant collision with another vehicle* (e.g., collisions at intersections, or when passing); E812—*other motor vehicle traffic accidents involving collision with a motor vehicle* (e.g., a collision with a parked, stopped, stalled, or disabled vehicle); E813—*motor vehicle traffic accidents involving collision with another [non-motor] vehicle* (e.g., a collision with a cyclist); E814—*motor vehicle traffic accidents involving collision with pedestrian*; E815—*other motor vehicle traffic accidents involving a collision on the highway* (e.g., striking an abutment, animal, or debris); and, E816—

motor vehicle traffic accidents due to loss of control, without a collision on the highway (e.g., losing control on a curve).

Of particular interest in this research is the medication information for individuals in the database with (selected types of) motor vehicle crashes, as a function of driver age. The analyses conducted by LeRoy and Morse examined only two broad categories—above and below age 50. Our efforts were principally devoted to a finer discrimination among older cohorts of crash-involved drivers, as described in the following pages.

First, our PharMetrics E-code study population was defined as those involved in the six crash types listed above, plus those with "unspecified" (E819) crash types, while continuing to exclude E-codes connoting "sources of external injury" deemed not relevant to the current project goals. Also, E-code suffixes of both "0" and "2" (the 4th digit in the diagnosis code), signifying drivers and motorcycle drivers, respectively, were included. Age was computed by subtracting the year of birth from the year of the E-code diagnosis. Cutpoints were then created at 5-year increments beginning at age 50 and increasing to age 85+, and frequencies were tabulated for each cohort. These data are presented in Table 1 for drivers of passenger vehicles and Table 2 for motorcycle drivers.

Another key step in this exercise was to ascertain which medications prescribed for the crash-involved individuals in the PharMetrics database were actually "current" at the time of a crash. Several data elements coded in the database were potentially relevant to this determination – "days supply," "quantity," "amount," and "Rx date." The date of each crash for each person represented in Tables 1 and 2 was also contained in the database.

If the "days supply" entry exceeded the interval between the Rx date and the crash date (allowing for up to three days for Rx overlap and processing delays) the prescription was deemed current. Of course, there is no guarantee that a person's medications were always taken on the prescribed schedule; but, proper compliance was assumed for the purposes of these analyses. Next, because insurance companies require that pharmacies provide the "days supply" information to receive payment for prescriptions, records without such an entry may be questioned. Records where the entry in the "days supply" field was missing or "0" were excluded.

Another crucial step involved the sorting and reclassification of every specific medication entered into the records of the PharMetrics study population—i.e., for which the prescription was current at the time a driver (or motorcycle driver) had a crash—into its "therapeutic drug class." This was necessary because PDI medications are identified at this level. Following LeRoy and Morse (2005), to qualify as a potentially driver-impairing medication, a drug *must be associated with central nervous system side effects, alter blood sugar levels, affect blood pressure, affect vision, or otherwise have the potential to interfere with driving skills.*

With reference to the case-control study reported by LeRoy and Morse, 90 drug classes were identified as potentially driver impairing. As determined in the present analyses, the (mean) number of "current" (at time of crash) PDIs taken by patients in different age groups in the PharMetrics database increased sharply for those 50 and older versus the 16 to 49 group; continued to climb as the patient database was truncated at successively older 5-year cohorts;

then leveled off when the "65 and older" threshold was reached. These findings are summarized below for all crash-involved drivers:

For drivers age: (*n* = _____)	16-49 (18,837)	50+ (3,737)	55+ (2,212)	60+ (1,208)	65+ (643)	70+ (474)	75+ (299)
The mean number of PDI meds was:	0.42	1.28	1.43	1.56	1.63	1.66	1.64

Next, we addressed a more specific question: *How many PDI meds were being taken by how many drivers* (assuming compliance with their prescription regimes) *within each age cohort of interest, at the time of their involvement in a motor vehicle crash?* With this information, we could consider which specific age cohorts to focus upon in continuing research including actual driver performance measurement; and which drugs (classes) deserve priority in such work, as well. The present analyses yielded the distribution of medications by age cohort displayed in Table 3. As indicated, the number of PDI drugs taken by individuals in the study population ranges from zero to 16 (absent 13 and 14). The proportions taking multiple (two or more) medications are highlighted.

As indicated, the rate of use of multiple PDI medications by crash-involved drivers climbs with age until leveling off at the 65- to 69-year-old cohort. Another perspective on these data is provided by the following graphics, which look more narrowly at the contrast between zero, one, and multiple drug usage. Figure 1 contrasts these relationships in a bar graph, while Figure 2 focuses still more closely on the changes in multiple drug use with driver age, as presently classified.

Table 1. Age distribution of crash-involved passenger vehicle drivers in E-code study population.

Diagnosis	16-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
E8110 - *motor vehicle traffic accidents involving re-entrant collision with another vehicle*	41	8	5	0	0	0	2	2	0
E8120 - *other motor vehicle traffic accidents involving collision with a motor vehicle*	9,783	741	529	292	93	95	95	51	20
E8130 - *motor vehicle traffic accidents involving collision with another [non-motor] vehicle*	1,725	156	111	56	18	22	26	19	12
E8140 - *motor vehicle traffic accidents involving collision with pedestrian*	56	9	2	4	0	2	2	1	0
E8150 - *other motor vehicle traffic accidents involving a collision on the highway*	528	42	23	16	6	0	0	0	0
E8160 - *motor vehicle traffic accidents due to loss of control, without a collision on the highway*	1,932	134	702	51	4	9	4	4	5
E8190 – *other; unspecified*	2,889	244	153	97	47	42	37	8	7
Total % (includes all codes within age cohort)	83.3	6.6	4.4	2.5	0.8	0.8	0.8	0.4	0.2
Total	**16,954**	**1,341**	**898**	**518**	**169**	**171**	**166**	**86**	**44**

Table 2. Age distribution of crash-involved motorcycle drivers in E-code study population.

Diagnosis	16-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
E8112 - *motor vehicle traffic accidents involving re-entrant collision with another vehicle*	4	1	0	1	0	0	0	0	0
E8122 - *other motor vehicle traffic accidents involving collision with a motor vehicle*	394	52	26	15	0	1	1	1	2
E8132 - *motor vehicle traffic accidents involving collision with another [non-motor] vehicle*	77	9	4	0	0	0	0	0	0
E8142 - *motor vehicle traffic accidents involving collision with pedestrian*	5	0	2	0	0	0	0	0	0
E8152 - *other motor vehicle traffic accidents involving a collision on the highway*	82	9	4	2	0	1	0	0	0
E8162 - *motor vehicle traffic accidents due to loss of control, without a collision on the highway*	682	65	40	19	1	1	0	0	0
E8192 – *other; unspecified*	639	56	34	13	0	2	0	0	0
Total % (includes all codes within age cohort)	83.8	8.6	4.9	2.2	--	--	--	--	--
Total	**1,883**	**192**	**110**	**50**	**1**	**5**	**1**	**1**	**2**

Table 3. Age cohort by number of current prescribed PDI medications, for all crash-involved drivers in PharMetrics database.

No. of PDI meds.	Age group													
	16-49		50-54		55-59		60-64		65-69		70-74		75+	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	14,721	78.1	827	54.2	499	49.7	240	42.5	63	37.3	67	38.2	98	32.8
1	2,274	12.1	287	18.8	199	19.8	135	23.9	36	21.3	37	21.1	82	27.4
2	922	4.9	182	11.9	119	11.9	65	11.5	32	18.9	21	12.0	42	14.0
3	437	2.3	106	7.0	72	7.3	48	8.5	20	11.8	22	12.6	29	9.7
4	220	1.2	59	3.9	40	3.9	24	4.2	6	3.6	15	8.6	23	7.7
5	122	0.6	31	2.0	35	3.5	27	4.8	5	2.9	1	0.6	15	5.0
6	67	0.4	15	1.0	16	1.6	9	1.6	2	1.2	5	2.9	4	1.3
7	30	0.2	6	0.4	10	1.0	4	0.7	3	1.8	3	1.7	3	1.0
8	23	0.1	3	0.2	6	0.6	6	1.0	2	1.2	1	0.6	3	1.0
9	5	0.0	2	0.1	5	0.5	3	0.5	0	--	2	1.1	.	.
10	9	0.0	4	0.3	1	0.1	2	0.4	0	--	0	--	.	.
11	6	0.0	0	--	0	--	2	0.4	0	--	1	0.6	.	.
12	.	.	3	0.2	1	0.1	0	--	0	--	0	--	.	.
15	1	0.0	0	--	0	--	0	--	0	--	0	--	.	.
16	.	.	0	--	1	0.1	0	--	0	--	0	--	.	.
2 or more	**1,842**	**9.8**	**411**	**27.0**	**306**	**30.5**	**190**	**33.6**	**70**	**41.4**	**71**	**40.6**	**119**	**39.8**
All	**18,837**		**1,525**		**1,004**		**565**		**169**		**175**		**299**	

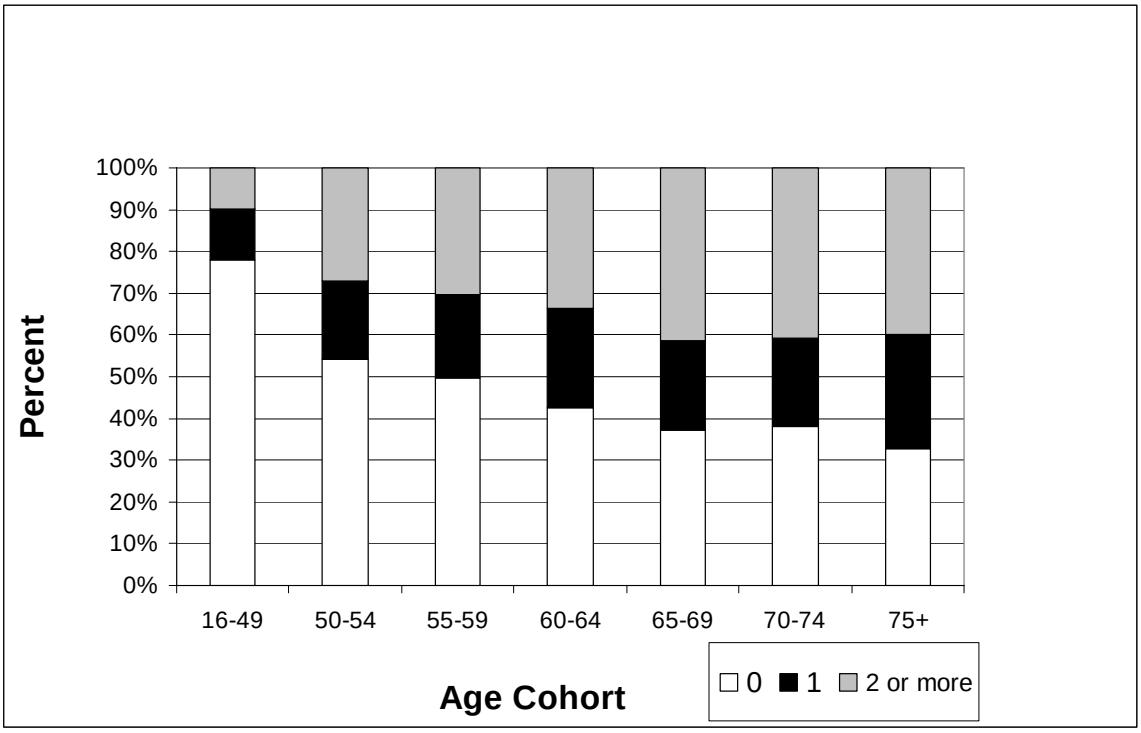

Figure 1. Proportions of crash-involved drivers within each age cohort taking none, versus one, versus multiple (2 or more) PDI medications at time of crash.

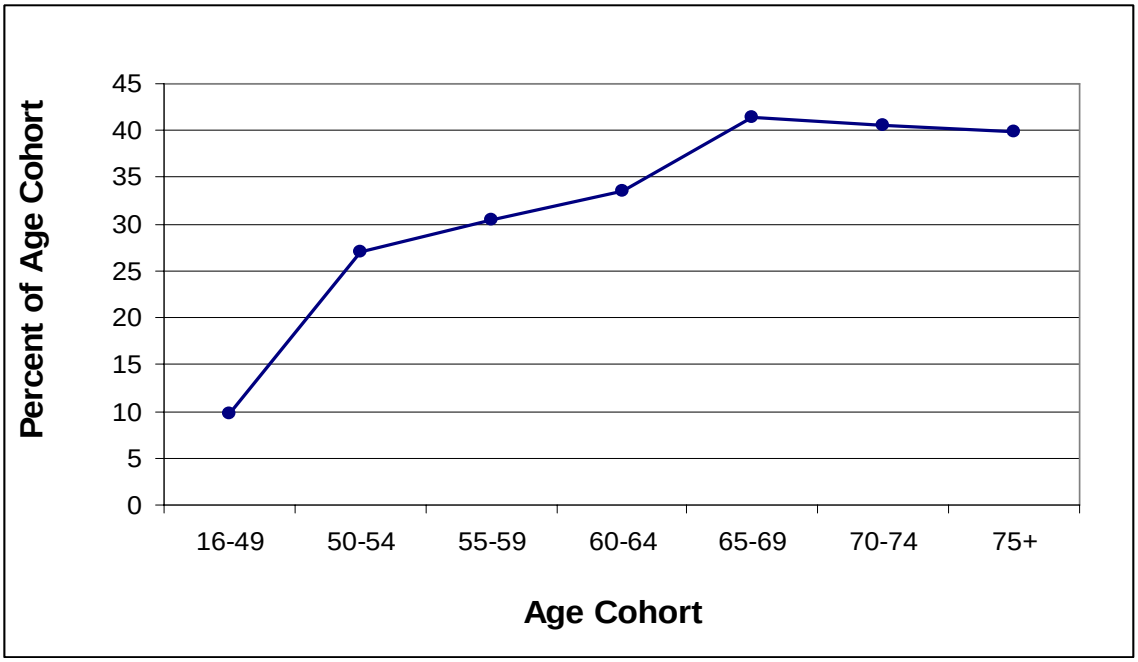

Figure 2. Proportion of crash-involved drivers in each age cohort taking multiple (2 or more) PDI medications at time of crash.

One question that may be asked with regard to these data is whether the number/proportion of crash-involved drivers taking multiple (two or more) medications increases significantly with increasing age. This may be framed in terms of a chi-square analysis, where the data from the "0', "1', and "2 or more' rows in Table 3 are entered as the observed values. Comparing these to the (calculated) expected values in each cell yields a X^2 test statistic of 1747.12, indicating a difference that is significant at $p < .001$ (d.f. = 12). This profoundly significant test result may be explained by the lower-than-expected use of PDI medications by the 16 to 49 age group and the higher-than-expected use by the older driver cohorts.

Another way of capturing this trend is to display the multipliers that reveal how many more crash-involved drivers than were expected are taking multiple PDI medications, in each group of (increasingly) older drivers:

For drivers aged:	50-54	55-59	60-64	65-69	70-74	75+
The multiplier indicating higher-than-expected use of PDI meds was:	2.02	2.29	2.52	3.11	3.04	2.99

At this point in the data mining exercise, we turned our attention from *how many* drugs were used by older, crash-involved drivers, to *what kind* of drugs. An analysis was performed to identify the top 25 most frequently prescribed therapeutic classes of PDI medications for selected age cohorts. In consideration of the data describing (1) the mean exposure to PDI meds by age group, noted earlier; and (2) the rate of multiple PDI drug use as a function of increasing age, shown above, the 50-and-older and 65-and-older groups were targeted for this analysis. That is, the 50-and-older group marks a clear departure from the data extracted for the 16 to 49 age group, while the data reported here also point to age 65 as a benchmark of sorts, in the changing pattern of PDI drug use (especially multiple PDI drugs) by crash-involved drivers.

The results shown in Tables 4 and 5 indicate that the top 25 therapeutic classes account for 88.7% of the PDI drugs prescribed for drivers 65 and older and 86.4% of the PDI drugs prescribed for 50-and-older drivers in the PharMetrics E-code study population.

The final activity in this task was to attempt to determine which specific combinations of PDI medications were most strongly represented among the crash-involved study population. Given the scope of this data mining exercise, it was necessary to narrow our focus to a limited number of age groups and a limited number of drugs-in-combination—while still yielding a result that would be useful to inform the research design for the subsequent pilot testing.

Referring back to Table 3 for a moment, the diminishing cell counts in successively older cohorts of drivers taking multiple (2 or more) medications is, in itself, a limiting factor in these continuing analyses. For example, there were 1,167 drivers in the study population taking multiple medications when the age cutoff is 50, but this number drops to 260 when considering only those individuals 65 and older. When examining the cell counts for 3, 4, 5, etc., PDI

medications taken concurrently, the frequencies also decline precipitously under any/all age categories.

Taking these trends into account, our continuing analyses were focused upon the row in Table 3 corresponding to two PDI medications. By seeking to identify relationships at this level of analysis, we can encompass as much data as possible that pertains to combinations of drugs associated with crash-involved drivers (i.e., in the PharMetrics E-code study population).

Table 4. Top 25 PDI medications prescribed for crash-involved drivers 65 and older in PharMetrics database where prescription is current at time of crash.

Therapeutic Drug Class	Frequency	Percent	Cumulative Frequency	Cumulative Percent
65 and older				
1. CALCIUM CHANNEL BLOCKING AGENTS	89	8.52	89	8.52
2. HYPOTENSIVES, ACE INHIBITORS	88	8.42	177	16.94
3. LIPOTROPICS	79	7.56	256	24.50
4. BETA-ADRENERGIC BLOCKING AGENTS	59	5.65	315	30.14
5. GASTRIC ACID SECRETION REDUCERS	56	5.36	371	35.50
6. NSAIDS, CYCLOOXYGENASE INHIBITOR - TYPE	51	4.88	422	40.38
7. THYROID HORMONES	50	4.78	472	45.17
8. ANALGESICS,NARCOTICS	49	4.69	521	49.86
9. HYPOGLYCEMICS, INSULIN-RELEASE STIMULANT TYPE	49	4.69	570	54.55
10. LOOP DIURETICS	41	3.92	611	58.47
11. ANTI-ANXIETY DRUGS	36	3.44	647	61.91
12. ALPHA-ADRENERGIC BLOCKING AGENTS	30	2.87	677	64.78
13. DIGITALIS GLYCOSIDES	25	2.39	702	67.18
14. SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRIS)	25	2.39	727	69.57
15. VASODILATORS,CORONARY	25	2.39	752	71.96
16. THIAZIDE AND RELATED DIURETICS	22	2.11	774	74.07
17. TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB	22	2.11	796	76.17
18. POTASSIUM SPARING DIURETICS IN COMBINATION	21	2.01	817	78.18
19. HYPOGLYCEMICS, BIGUANIDE TYPE (NON-SULFONYLUREAS)	20	1.91	837	80.10
20. SEDATIVE-HYPNOTICS,NON-BARBITURATE	20	1.91	857	82.01
21. ANTICONVULSANTS	15	1.44	872	83.44
22. BETA-ADRENERGIC AGENTS	15	1.44	887	84.88
23. SKELETAL MUSCLE RELAXANTS	15	1.44	902	86.32
24. HYPOTENSIVES,ANGIOTENSIN RECEPTOR ANTAGONIST	13	1.24	915	87.56
25. HYPERURICEMIA TX - PURINE INHIBITORS	12	1.15	927	88.71

Table 5. Top 25 PDI medications prescribed for crash-involved drivers 50 and older in PharMetrics database where prescription is current at time of crash.

Therapeutic Drug Class	Frequency	Percent	Cumulative Frequency	Cumulative Percent
50 and older				
1. LIPOTROPICS	367	7.68	367	7.68
2. HYPOTENSIVES, ACE INHIBITORS	364	7.62	731	15.30
3. NSAIDS, CYCLOOXYGENASE INHIBITOR – TYPE	287	6.01	1018	21.30
4. GASTRIC ACID SECRETION REDUCERS	283	5.92	1301	27.22
5. CALCIUM CHANNEL BLOCKING AGENTS	281	5.88	1582	33.10
6. ANALGESICS, NARCOTICS	271	5.67	1853	38.77
7. BETA-ADRENERGIC BLOCKING AGENTS	242	5.06	2095	43.84
8. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	226	4.73	2321	48.57
9. THYROID HORMONES	208	4.35	2529	52.92
10. HYPOGLYCEMICS, INSULIN-RELEASE STIMULANT TYPE	175	3.66	2704	56.58
11. ANTI-ANXIETY DRUGS	173	3.62	2877	60.20
12. ANTICONVULSANTS	126	2.64	3003	62.84
13. THIAZIDE AND RELATED DIURETICS	112	2.34	3115	65.18
14. TRICYCLIC ANTIDEPRESSANTS & REL. NON-SEL. RU-INHIB.	112	2.34	3227	67.52
15. SKELETAL MUSCLE RELAXANTS	110	2.30	3337	69.83
16. HYPOGLYCEMICS, BIGUANIDE TYPE (NON-SULFONYLUREAS)	104	2.18	3441	72.00
17. POTASSIUM SPARING DIURETICS IN COMBINATION	104	2.18	3545	74.18
18. LOOP DIURETICS	100	2.09	3645	76.27
19. BETA-ADRENERGIC AGENTS	83	1.74	3728	78.01
20. ALPHA-ADRENERGIC BLOCKING AGENTS	79	1.65	3807	79.66
21. HYPOTENSIVES, ANGIOTENSIN RECEPTOR ANTAGONIST	75	1.57	3882	81.23
22. SEDATIVE-HYPNOTICS, NON-BARBITURATE	70	1.46	3952	82.70
23. SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS (SARIS)	63	1.32	4015	84.01
24. DIGITALIS GLYCOSIDES	57	1.19	4072	85.21
25. INSULINS	57	1.19	4129	86.40

Maintaining a focus on the 65-and-older group is attractive from the standpoint that—based on the present analyses—polypharmacy among crash-involved drivers appears to level off at this age. It also is a widely accepted cutoff for designating "older" drivers in the technical and popular literature on this subject. Inspection of Tables 4 and 5, however, reveals some differences in the prevalence of medications taken by the 65-and-older group versus a group that includes younger (50-and-older) drivers. While the primary anti-hypertensives are second in prevalence among both cohorts, lipotropics (used to lower blood cholesterol) are more prevalent among middle-aged drivers while medications to relieve angina and prevent heart attacks (calcium channel blockers and beta blockers) are more prevalent among drivers 65 and older.

Given these contrasts, it seemed valuable to include both the 50-and-older and the 65-and-older groups in the remaining analyses to determine which specific combinations of PDI medications were most commonly prescribed to crash-involved drivers. The leading combinations follow in Tables 6 and 7, in order of decreasing frequency of database entries (percent calculations rounded to nearest tenth).

Table 6. Most frequent two-PDI drug combinations for crash-involved drivers 65 and older.

Drug Combination	n	%
Hypotensives (Angiotensin-converting enzyme [ACE] Inhibitors) + Antidepressants	4	0.6
Hypotensives (ACE Inhibitors) + Thyroid Hormones	4	0.6
Hypotensives (ACE Inhibitors) + Lipotropics (HMG/COA Reductase Inhibitors)	3	0.5
Hypotensives (ACE Inhibitors) + Non-steroidal anti-inflammatory drugs (NSAIDS)	2	0.3
Diuretics + NSAIDS	2	0.3
Diuretics + Cardiotonic Drugs	2	0.3
Benzodiazepines (Anxiolytic/Sedative/Hypnotic) + Lipotropics (HMG/COA Reductase Inhibitors)	2	0.3
Beta-Adrenergic Blocking Agents + Lipotropics (HMG/COA Reductase Inhibitors)	2	0.3
Benzodiazepines (Anxiolytic/Sedative/Hypnotic) + Beta-Adrenergic Blocking Agents	2	0.3
Hypotensives (ACE Inhibitors) + Beta-Adrenergic Blocking Agents	2	0.3
Hypotensives (ACE Inhibitors) + Selective Serotonin Reuptake Inhibitors (SSRIS)	2	0.3
NSAIDS + Calcium Channel Blocking Agents	2	0.3
Diuretics (Loop) + Digitalis Glycosides	2	0.3
Hypotensives (ACE Inhibitors) + Gastric Acid Secretion Reducers	2	0.3
Hypotensives (ACE Inhibitors) + Calcium Channel Blocking Agents	2	0.3
Analgesic/Narcotics + Gastric Acid Secretion Reducers	2	0.3

The combinations of medications highlighted in Tables 6 and 7 are not exhaustive. Specifically, the combinations of medications listed represent a common fraction of the total 2-PDI counts for both the 65-and-older group (95) and the 50-and-older group (461) -- approximately 40% in each case.

While the numbers and percentages in these lists are small in absolute terms, it should be noted that these values pertain exclusively to the two-drug combinations—not the phenomenon of polypharmacy, more generally—among older, crash-involved drivers in this database. Also, according to the present analyses, from one-third to one-half of crash-involved drivers in each cohort older than 50 were taking no PDI medications at all.

With these caveats, the results of this project activity supported a decision to concentrate on two-PDI drug combinations in the subsequent data collection activities. It was also concluded that a primary focus on medications to lower blood pressure (the hypotensives) was warranted. In fact, a pilot study examining the effects on driving performance of this drug class in combination with certain other PDI medications represented in the lists above – e.g., lipotropics, beta blockers, calcium channel blockers, NSAIDS, SSRIs, and gastric acid secretion reducers – emerged as the research strategy that comports best with these data, while addressing overall project goals.

Table 7. Most frequent 2-PDI drug combinations for crash-involved drivers 50 and older.

Drug Combination	n	%
Hypotensives (ACE Inhibitors) + Calcium Channel Blocking Agents	12	0.3
Diuretics + Beta-Adrenergic Blocking Agents	11	0.3
Hypotensives (ACE Inhibitors) + Antidepressants	10	0.3
Antidepressants + Benzodiazepines (Anxiolytic/Sedative/Hypnotic)	10	0.3
NSAIDS + Opiate Agonists	9	0.2
Analgesic/Narcotics + NSAIDS	9	0.2
Antidepressants + Lipotropics (HMG/COA Reductase Inhibitors)	9	0.2
Hypotensives (ACE Inhibitors) + Beta-Adrenergic Blocking Agents	9	0.2
Hypoglycemics (Biguanide Type) + Hypoglycemics (Sulfonylurea Type)	8	0.2
Opiate Agonists + Skeletal Muscle Relaxants	8	0.2
Hypotensives (ACE Inhibitors) + Dihydropyridines	8	0.2
Analgesic/Narcotics + Skeletal Muscle Relaxants	8	0.2
Hypoglycemics (Insulin Release Stimulant Type) + Hypoglycemics (Non-sulfonylureas)	8	0.2
Lipotropics + Calcium Channel Blocking Agents	7	0.2
Hypotensives (ACE Inhibitors) + Thyroid Hormones	7	0.2
Beta-Adrenergic Blocking Agents + Lipotropics (HMG/COA Reductase Inhibitors)	7	0.2
Hypotensives (ACE Inhibitors) + Lipotropics (HMG/COA Reductase Inhibitors)	7	0.2
Anti-Anxiety Drugs + Selective Serotonin Reuptake Inhibitor (SSRIS)	6	0.2
Diuretics (Potassium Sparing) + Beta-Adrenergic Blocking Agents	6	0.2
Gastric Acid Secretion Reducers + NSAIDS	6	0.2
Hypotensives (ACE Inhibitors) + Hypoglycemics (Insulin Release Stimulant Type)	6	0.2
Antidepressants + Proton-Pump Inhibitors	6	0.2
Beta-Adrenergic Blocking Agents + Dihydropyridines	6	0.2
NSAIDS + Histamine H2-Antagonists	6	0.2
Analgesic/Narcotics + Lipotropics	5	0.1
Hypotensives (ACE Inhibitors) + Gastric Acid Secretion Reducers	5	0.1
Beta-Adrenergic Blocking Agents + Gastric Acid Secretion Reducers	5	0.1
Hypotensives (ACE Inhibitors) + Selective Serotonin Reuptake Inhibitors (SSRIS)	5	0.1
Lipotropics + Selective Serotonin Reuptake Inhibitors (SSRIS)	5	0.1
Antidepressants + Beta-Adrenergic Blocking Agents	5	0.1
Antidepressants + NSAIDS	5	0.1
Antidepressants + Thyroid Agents	5	0.1
Hypotensives (ACE Inhibitors) + Hypoglycemics (Sulfonylureas)	5	0.1
Beta-Adrenergic Blocking Agents + Thyroid Agents	5	0.1
Diuretics + Calcium Channel Blocking Agents	5	0.1
Antidepressants + Opiate Agonists	5	0.1

Pilot Testing Strategies to Study Polypharmacy and Driving

Research Methods

The pilot study included the collection of data describing sample characteristics for forty-four (44) active, older drivers recruited in residential communities in Delaware and Maryland, including functional status measures and medication usage, followed by driving evaluation measures including an on-road examination by an occupational therapist/certified driver rehabilitation specialist (OT/CDRS) and brake response time measures using an instrumented vehicle. For a subsample of five individuals, video, GPS and speed recordings in their own, private cars were also carried out to examine the variability in selected behaviors—surrogates of driver attention/distraction, plus speed choice—during independent driving versus drives with the OT, under comparable conditions.

Sample Recruitment

The recruitment of study participants took place at the Cokesbury Village Continuing Care Retirement Center in Hockessin, DE, a member of the Peninsula United Methodist Homes network; and at the Oak Crest Village and Charlestown campuses of the Erickson Retirement Communities network, located respectively in Parkville, MD, and Catonsville, MD. As noted in the Acknowledgements section of this report, the support of management in these facilities was absolutely essential to successful recruitment and to the conduct of this research. So, too, were the efforts of the Rehabilitation Services managers and staff, not only by engaging and maintaining contact with the participants through the multistage data collection efforts, but also in the actual administration of a computer-based test battery to obtain measures of visual, physical, and cognitive function for the study sample.

Following review and approval of planned recruitment methods by the Institutional Review Board at the University of North Carolina, Chapel Hill, flyers were distributed at the residential facilities announcing the research opportunity, outlining inclusion criteria for the study, and providing a point of contact for more information. An “active” driver was defined as a person who drivers at least 50 miles and/or 3 days or more per week. The combinations of medications sought among the study sample—reflecting the earlier data mining activity in this project—included an antihypertensive agent *and* a drug from any *one* of these classes: SSRIs; gastric acid secretion reducers; lipotropics (non-statins; mainly prescribed for obesity); HMG-COA inhibitors (statins; mainly prescribed to lower cholesterol); or NSAIDs (prescribed for pain). The point of contact during recruitment for more information about study participation was the *TransAnalytics* Principal Investigator (PI). Examples of recruitment material are shown in Appendix A.

In addition, a small number of controls were sought as study participants, who were not taking <u>any</u> prescribed drugs that have been identified as PDI medications; the use of non-PDI prescription drugs and/or over-the-counter remedies (vitamins, herbals, etc.) did not disqualify individuals from participation in this group. Despite protracted efforts, only four individuals (of the total of 44 study participants) meeting the criteria for controls could be enlisted in the study.

In fact, there was considerable difficulty in recruiting older drivers taking the medication classes of interest in this research. After fewer than a dozen individuals responded to the first "wave" of flyers distributed in residents' mailboxes, a later questionnaire was distributed by residential community staff, to attempt to learn the reasons for the low response rate, so a follow up effort might be more successful. This questionnaire is shown in Appendix B.

Anonymous feedback was requested. The questionnaire provided 11 potential reasons for non-participation, plus space to write in any other reasons. Residents were asked to check all reasons that pertained to their decision to decline participation and to list any other reasons they chose not to participate. A total of 81 residents completed and returned the survey. The number and percentage of respondents who chose each reason is presented in Table 8 below.

Table 8. CCRC residents' reasons for not participating in this research study.

Reason	Frequency (and percent) of respondents (n=81)
I did not qualify for the study based on the medications I am taking.	16 (19.8%)
I do not drive enough to qualify for the study.	25 (30.9%)
I was out of town.	3 (3.7%)
I was too busy; I did not want to commit to the time required for study participation (3 hours).	13 (16%)
I did not feel the incentive payment ($100) offered for study participation was enough.	2 (2.5%)
I did not want to reveal my medication usage or medication history.	1 (1.2%)
I did not want to drive with a stranger (for the driving evaluation part of the study).	1 (1.2%)
I did not want to drive an unfamiliar car (for the evaluation part of the study).	7 (8.6%)
I did not want instrumentation that would record my driving behavior to be installed in my car.	8 (9.9%)
I did not trust that the results of my driving evaluation would remain confidential.	2 (2.5%)
I was worried that the results of my driving evaluation would be reported to the DMV	2 (2.5%)
Other	38 (46.9%)

The 38 "other" reasons provided by CCRC residents for not participating in the study are presented in Table 9 on the next page, grouped into similar response types.

Table 9. CCRC residents' comments explaining reasons for non-participation.

Comments related to lack of interest in study (n=4)	
3	Not interested.
1	My available time is too uncertain. Also, my interest in taking such a test was nil regardless of any monetary incentive.
Comments related to not owning a car or driving anymore (n=6)	
1	I do not own a car. My daughter drives me where I need to go.
1	I sold my car and allowed license to lapse before moving here.
1	I gave my car away six years ago. One of my sons needed it more than I did. I have not driven since then and now have a license but husband says I no longer drive.
1	I stopped driving in March 2002 due to poor hearing and wet macular degeneration in both eyes.
1	I don't have a car. I don't drive anymore.
1	Have macular degeneration in my right eye. It came all at once. I decided myself I might be a risky driver so I gave my car [away] and no longer drive. I felt I should practice what I have always preached. I am 92 years old.
Other issues surrounding driving (n=1)	
1	I thought the test would be given on a computer rather than actual driving.
Comments related to not being informed about the study/not receiving a flyer (n=11)	
4	No flyer received. *or* I do not remember getting the flyer.
1	Just never heard of it
1	Don't recall receiving questionnaire
1	We were not asked to participate in the study as we did not live here.
1	We cannot recall receiving this flyer.
1	I did not receive the flyer asking me to join the study. Most likely I would have joined.
1	I did not have full information. Also I do not have the extra time right now.
1	Did not feel original explanation explained enough. Unclear what the benefit was.
Comments relating to lack of follow-up in recruiting (n=2)	
1	Nobody bothered to answer my volunteer.
1	I think I did sign up for this but it has been several months since that moment. Sorry you haven't gotten a good response, as evidenced by the need for this follow-up.
Medication related comments (n=4)	
1	We do not take any medications on a regular basis, then only when absolutely needed.
1	I originally signed up, but was told my medication might disqualify me. When I didn't hear anything for a long time, I assumed I would not qualify by then we had made plans to go on some visits and were very busy so I had to turn down the offer to participate
1	I am not on medication--was that a condition for participation?
1	I don't take medications.
Conflicts with other activities (n=3)	
1	This may have happened as I was moving in and trying to get acclimated. It took awhile to settle in and find my way about.
1	I have too many dentist/doctor/surgeon appointments! Surgery scheduled Jan '07.
1	I was involved with some personal family matters at that time.
Unknown/non-specific reasons for not participating (n=7)	

Follow up recruitment efforts were initiated, including an appeal by the PI in a "village meeting" at the Cokesbury Village CCRC. At the Erickson communities, a vigorous, coordinated effort by the Erickson Research Foundation and the Rehabilitation Services department was undertaken to "get the word out." As a result of these efforts, study recruitment goals for drivers using multiple medications in the drug classes of interest were met, and data collection activities were subsequently carried out during the summer and fall of 2006 at Cokesbury Village, and during the spring and summer of 2007 at the Erickson communities.

Data collection was accomplished only through the dedicated efforts of the Rehab Services staff at each residential community, complemented by the specific expertise of a visiting pharmacist who conducted medication reviews, and an occupational therapist/ certified driving rehabilitation specialist (OT/CDRS) who performed on-road driving evaluations as a consultant to this project. Across each participating facility, a common, prescribed series of steps were followed: pre-qualification, functional testing, medication review, and behind-the-wheel evaluation. These activities are described in more detail below.

Pre-qualification

Each prospective study participant was pre-qualified by verbally reviewing his/her current prescriptions in relation to a prepared list of desired drug classes, and common brands within class, through initial telephone contact with the PI; *or*, the initial contact for some participants was with the Rehab manager, onsite at the residential facility, who evaluated their suitability for the study using the same reference list.

Those who were enrolled in the study were advised that they would be required to (a) read a detailed informed consent agreement and agree to the study procedures described therein, if they wished to enroll in the study; (b) complete a set of tests and exercises administered on a computer, requiring approximately one-half hour (but not requiring familiarity with how to use a computer per se); (c) complete a review of all medications they are currently taking, via consultation with a registered pharmacist who would come to their residence, and also request a printout of their current prescriptions from their own pharmacist; (d) complete a behind-the-wheel examination by an occupational therapist in a dual-brake-equipped, mid-size passenger vehicle (Ford Taurus), conducted on streets/highways in the vicinity of their residence; and (e) optionally, to allow the research team to install instrumentation in their own vehicles that would be small and unobtrusive, but would capture on video a record of when, where, and how they drove. All prospective study participants were given a strict assurance of confidentiality, whereby no results would be shared with state government officials or any other parties unless required by law (e.g., in the event of a crash); and of anonymity, whereby participants would be identified via codes instead of names, and driving evaluation data would be reported only in the aggregate.

All questions about the study were answered, and the offer of $100 compensation for study participation, as stated in the recruitment flyers, was reiterated at this time.

Functional Testing

After receiving the prequalification information, the people who remained interested in study defined the participant list for each facility. This list was maintained and updated by the rehab manager in cooperation with the PI. Working from this list, the rehab manager first contacted each participant to arrange a convenient time for him/her to complete the computer-based functional tests in the offices of the Rehab Services unit in each facility.

The functional tests applied in this research were carried out on a PC using a screening program, the DrivingHealth Inventory. The DHI includes measures of physical ability (head/neck mobility, leg strength/mobility/balance) and cognitive ability (visual search/divided attention, visuospatial ability/visual closure, visual information processing speed/divided attention, working memory) validated as at-fault crash predictors in prior research sponsored by NHTSA (see Staplin, Lococo, Gish, & Decina, 2003); plus, two vision measures (high- and low-contrast static acuity) suggested by existing license policy in the United States and by other research (Janke, 1991).

The PI provided on-site training to each facility's Rehab Manager and staff in the use of the DHI computer program. Functional status data for each older driver enrolled in the study were stored on the facilities' PCs until removed by the PI for analysis after data collection was completed. Performance on the measures of functional ability had no bearing on continued study participation; all participants who completed this activity continued to the next stage (medication review).

Medication Review

After completing the functional testing, each participant was introduced (or made aware of a pending contact from) the consulting pharmacist, by the facility Rehab manager. The instructions participants received about the medication review specified that all prescription medications, all over-the-counter medications, and any vitamins or supplements were to be placed in a "brown bag" and brought for pharmacist review at an appointed time. It was stated that these should include, "*every over-the-counter and prescription medication, including pills, liquids, drops, creams/lotions, and inhalants.*" It was further specified that participants should, "*include medicines that you take for any medical condition that the doctor gave you or you got from a pharmacy with a prescription, or any other prescription medication that you use and got from a friend or family member. Also, put medications in the bag that you use that were bought at a drug store, grocery store, convenience store, etc., without a prescription, or other non-prescription medication that you use that you got from a friend or family member.*"

Each participant brought his/her bag of medications to the appointed time/place for review by the visiting pharmacist, who inquired whether the medications in the bag were still being taken, confirmed the precise regime (dose and schedule information), and entered all information on a prepared form (see Appendix C). The pharmacist provided immediate feedback to the participant if perceived to be in his/her best interest, or if requested at that time; otherwise, participants were provided with individualized feedback on their medication reviews at the conclusion of the project.

Behind-the-Wheel Driving Evaluation

The behind-the-wheel driving evaluation was scheduled by the OT/CDRS with each participant after completion of his/her medication review. At the appointed time, the OT/CDRS met the participant at an agreed-upon location at the residential community, confirmed that he/she held a valid driver's license, and recorded (based on self-report) what medications had been taken within the previous 12 hours. The individual's past medical history, plus driving history and driving restrictions, were also queried. This information, plus the date, time, and road/weather conditions during the evaluation, was recorded on a form developed by the OT/CDRS to score the evaluation outcomes (see Appendix D).

This form included varying numbers of items; each was scored individually as appropriate to behaviors observed under the categories of *vehicle entry, initiating driving/starting procedures, general driving, controlled intersections, uncontrolled intersections, turns, visual skills,* and *lot parking*. An overall rating was also assigned, and any/all interventions required by the OT/CDRS for safety during the driving evaluation were noted. At the end of the form, two items were included to record participants' ratings (7-point bipolar scale) of familiarity with, and frequency of exposure to, the roads traveled on during the driving evaluation. The OT/CDRS added comments and suggestions for improved driving habits on a separate page; these were reviewed with the individual after returning safely to the residential community.

The participant and evaluator proceeded to a parking lot on the premises for familiarization with the test vehicle, and to allow the OT/CDRS to perform a "closed course" evaluation of basic driving skills before leaving the grounds to drive in traffic. The test vehicle, a dual-brake-equipped 1996 Ford Taurus sedan, was loaned to TransAnalytics by NHTSA for this data collection activity.

Additional modifications and instrumentation of the test vehicle were carried out (1) to provide for the safety of the evaluator and examinee, and (2) to collect data to be used in comparing the attention of drivers during the evaluation versus driving alone in their own cars. In the first case, this included a second, inside rear-view mirror installed at the upper right of the windshield, so the OT/CDRS could monitor traffic behind the vehicle when riding in the passenger seat during an on-road evaluation. Special instrumentation included a camera box, with a driver (face) camera and forward road camera, plus a GPS receiver that was attached via suction cups in the center of the windshield just below and behind the rearview mirror. A lockable metal box containing a digital video recorder, a video processor, a DC-DC converter, and a voltage-controlled switch, was placed behind or under the front seat.

Figure 3 presents photos of the vehicle used for on-road testing, plus the items of equipment noted above. The upper left quadrant in Figure 3 shows the test vehicle.

Figure 3. Test vehicle, face and road camera box, and video recording equipment.

The right half of Figure 3 contains a view of the camera box installed on the windshield (upper right) and of the inside of this enclosure (lower right). The GPS antenna is located in the top left of the camera box, the face camera is located underneath the antenna, and the road camera is to the right. The lower left quadrant shows a picture of the inside of the recording box with digital video recorder, video processor, a power converter, and voltage-controlled switch (to activate the recorder).

The photo above of the camera box mounted below the inside rearview mirror shows how this unit appeared to each older driver evaluated in this study. Participants reported that this device did not obstruct their view or distract them during the driving evaluation. The photos of the components within the camera and recording boxes also show the appearance of these units (during fabrication; not as seen by study participants) but do not clearly reveal their inter-connections or functionality. For this information, refer to the schematic drawings in Figures 4 and 5 on the following page.

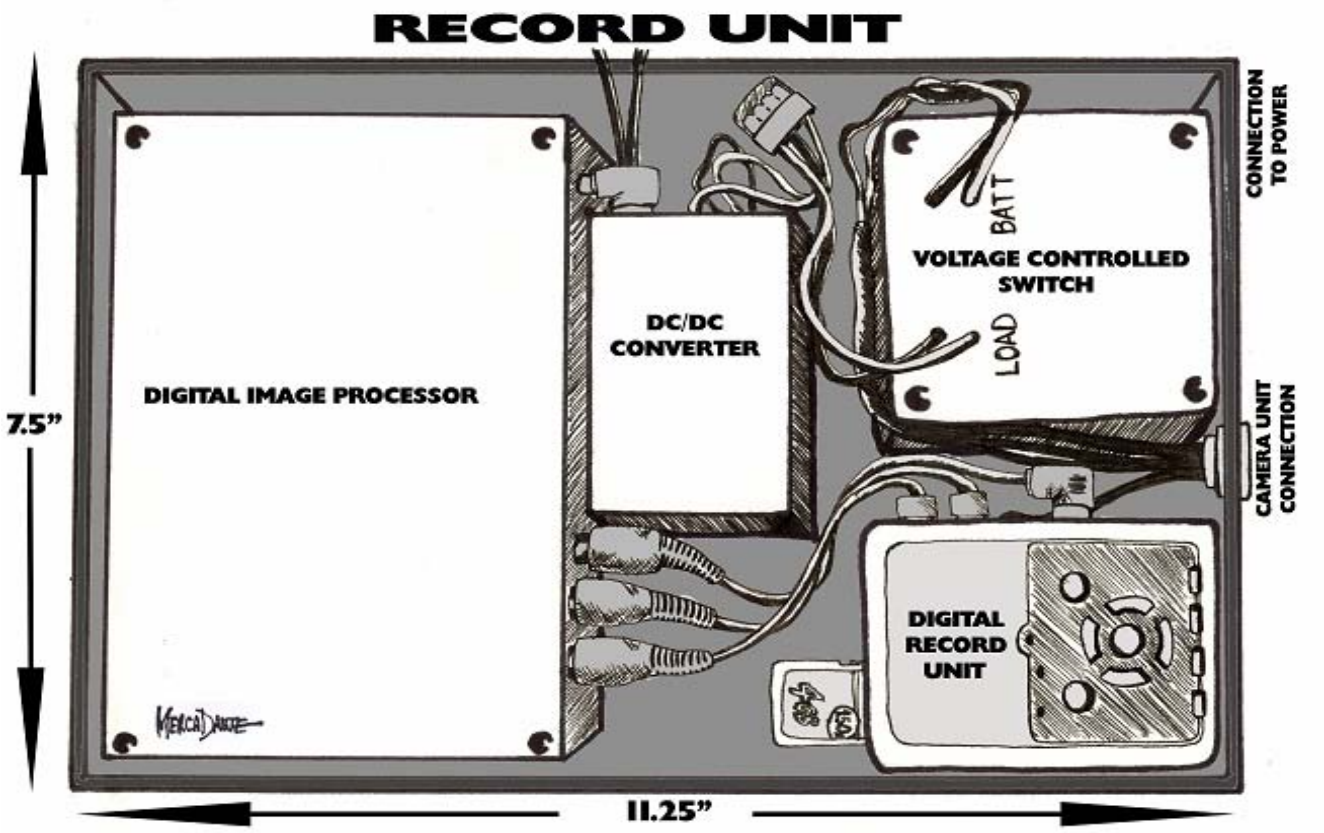

Figure 4. Video recording unit for the driver and road cameras in the test vehicle.

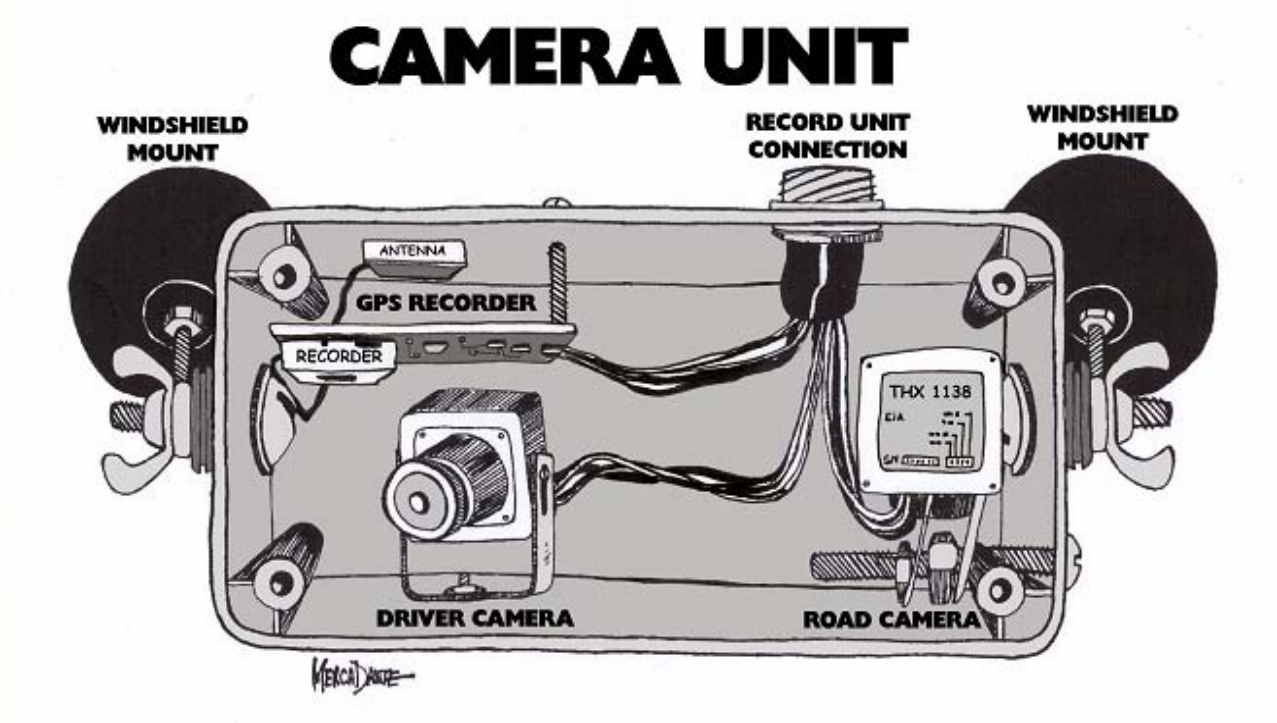

Figure 5. Driver and road camera, plus GPS unit, behind translucent faceplate.

The vehicle instrumentation described above was integrated with one additional data stream, namely, a continuous recording of speed, and brake and throttle position obtained through the on-board diagnostic (OBD) port that is available on all post-1995 vehicles sold in the United States. A commercially-available "car chip" was plugged into this port on the Ford Taurus test vehicle during the OT/CDRS driving evaluations.

Thus, the test vehicle instrumentation system, powered from a 12V DC adapter plugged into the cigarette lighter, was designed to record three types of data, as follows:

- Video: ASF format with 704x496 resolution and 12 Hz frame rate. Each trip is recorded into 10- to 100-second snippets (depending on the amount of motion in the video) which are later combined and rendered in post-processing to produce single clips for subsequent video coding analysis. The recorders were set to start recording automatically when powered on and stop recording when no motion was detected in the driver face view camera for at least 30 seconds.
- GPS: Standard NMEA sentences ($GPGGA for GPS time, latitude, longitude, heading, and $GPVTG for speed) were logged. The lat/long coordinates can be converted to KML format for display on Google Maps.
- OBD: Using the on-board diagnostics capability, the test vehicle speed (at 1 Hz sample rate), throttle position (1 sample every 5 seconds), and engine speed (1 sample every 5 seconds) were logged. The date/time was recorded at the beginning and end of each trip, requiring intermediate times to be interpolated.

These data sources were manually linked using date and time stamps common to each source. Video and OBD times were synchronized to an Internet time server prior to data collection; GPS time was logged directly from GPS satellites.

The OT/CDRS checked to see that all on-board equipment was functioning before meeting the examinees each day. As discussed later, the reliability of some components – the GPS unit, in particular – was not as good as the others, however, and this affected (but did not rule out) the planned comparisons of selected individuals' driving habits when in their own cars versus when driving the test vehicle with the evaluator riding in the passenger seat. It should be noted that *the function of the on-board instrumentation did not impact the OT/CDRS evaluation data in any way*; this outcome was based solely on the scores assigned on the evaluation form during the on-road test.

To begin the behind-the-wheel evaluation, the OT/CDRS typically drove the test vehicle to a location near the residential community that marked the beginning of a pre-planned route, which would be followed by every study participant from a given facility. After moving to the passenger seat, the OT/CDRS provided verbal driving directions for the remainder of the test route. Test routes were designed to include an initial segment of low-demand, residential driving, where a brake response time task (described below) was performed; this lead to driving on arterial routes where participants would encounter stop-sign- and signal-controlled intersections and the potential for conflict with other vehicles would increase significantly. One test route was developed in the Hockessin, DE, vicinity and another in the Parkville, MD, vicinity. Figures 6 and 7 show the roads in each route, including those segments designated for brake response time trials.

Figure 6. Roads traversed on test route for driving evaluations in the vicinity of Hockessin, DE.

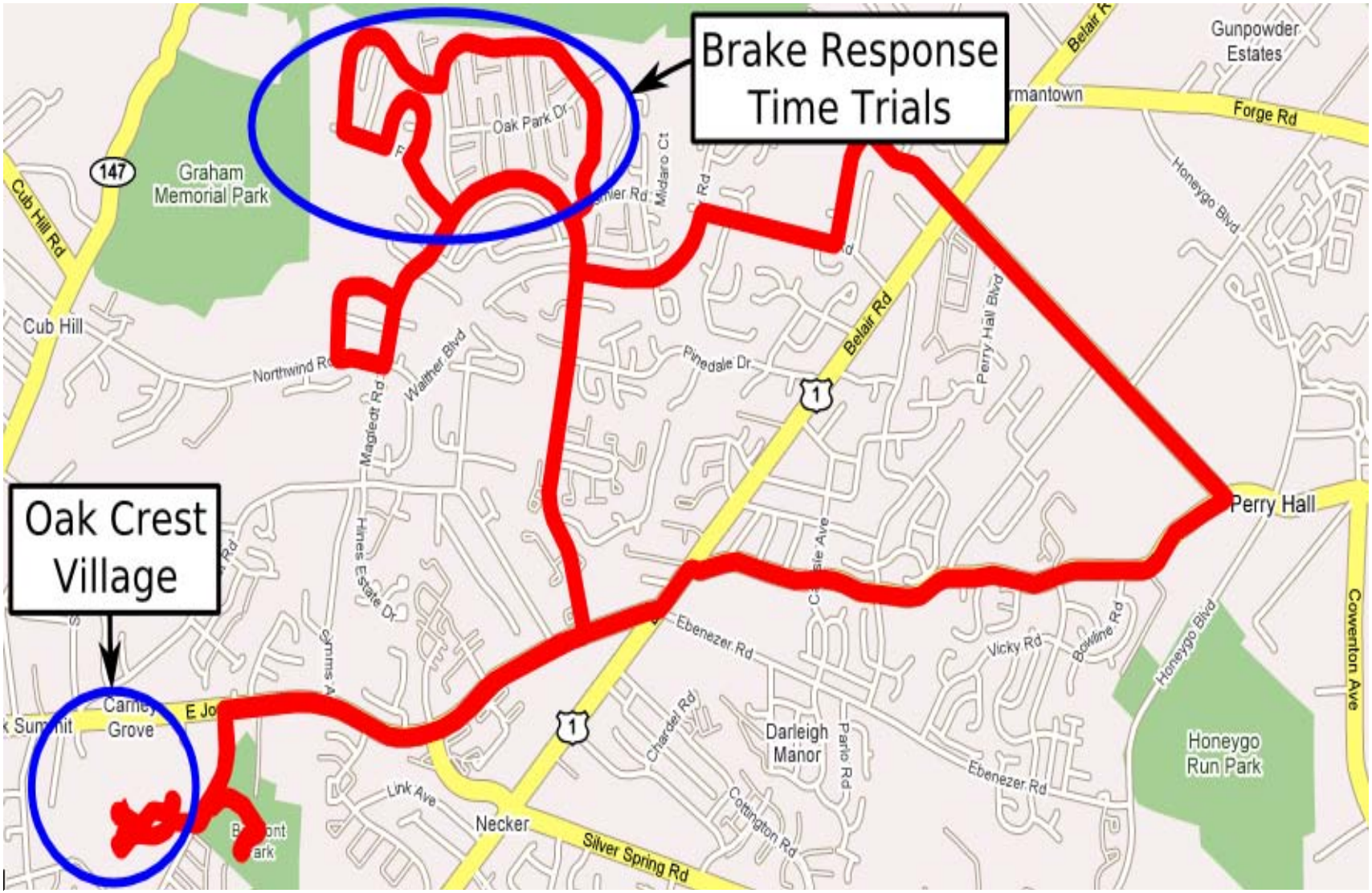

Figure 7. Roads traversed on test route for driving evaluations in the vicinity of Parkville, MD.

The brake response time trials were designed to provide an objective measure of performance (and possible differentiator among the study participants) to complement the driving evaluation scores. This was obtained by placing a small (4 in wide x 3 in high x 3 in deep) enclosure on the dashboard at the A-pillar, in the lower left corner of the windshield. An LCD faced the driver from the inside back of this enclosure. This display, which was connected to an onboard computer, was otherwise blank. But when triggered by the OT/CDRS in the passenger seat, via a button-push mechanism that was out of the driver's sight, one of two images would appear on the display: A "stop ahead" warning sign (MUTCD W3-1), or a stop sign (MUTCD R1-1), as shown below:

W3-1

R1-1

The OT/CDRS previewed these displays to each study participant, explaining that these displays would appear unexpectedly as he/she was driving in the residential area. In some cases, only the stop sign would appear, while in other cases the warning sign would appear first with the stop sign following a few seconds later. Participants were instructed to remove their right foot from the accelerator and press the brake as quickly as possible *only when the stop sign appeared*. On trials when the warning sign appeared, their instructions were to wait to respond until the stop sign was in view. A relay was installed on the brake switch circuit to record the RT data using the onboard computer.

It was hypothesized that (multiple) medication usage might affect the ability to inhibit a planned response, as well as having an effect on the actual brake response time to the stop sign presentation. Thus, both the number of errors (inappropriate brake responses to warning sign stimulus) and the brake RT on the un-alerted trials were scored. A photo of the (stop sign) display as seen by a study participant is shown in Figure 8.

Six practice trials were allowed while the test vehicle was parked, including an equal mix of "alerted" (warning sign followed by stop sign) and "un-alerted" (stop sign only) stimulus presentations. When confident that the study participant understood the instructions, the test drive resumed in the residential neighborhood, and the OT/CDRS triggered 3 more un-alerted and 3 more un-alerted trials while the driver was navigating through the neighborhood. Trial order was pre-programmed into the onboard computer. The OT/CDRS sought to trigger the stimulus presentations at the same exact locations for each study participant, but could alter the protocol if needed due to an unusual event, such as a homeowner backing out of a driveway in potential conflict with the test vehicle. All stimulus presentations for the brake response trials

took place on the same streets, in the same residential neighborhoods (i.e., specific to each source community), and under the same conditions of weather (clear and dry) and traffic (none).

After completing the brake response time trials, the OT/CDRS provided verbal directions to the study participant that lead him/her out of the residential neighborhood, onto streets where speed limits were higher, a wider range of traffic control devices were present and maneuvers (e.g., turns) was required, and where there was a progressively higher probability of encounters (and potential conflicts) with other traffic. Throughout each driving evaluation, the OT/CDRS continuously noted scored participants' behavior as per the form included in Appendix D.

Figure 8. LCD display on dashboard, used for brake response time measure.

Each test drive lasted approximately 45 minutes, from the time the OT/CDRS and a study participant left the residential community, drove to the residential neighborhood and changed positions in the test vehicle, practiced and completed the brake response time trials, then proceeded with the behind-the-wheel evaluation and eventually arrived back at the CCRC, either Cokesbury Village or Oak Crest Village. At that time, the driving evaluator reviewed the individual's results with him/her, providing suggestions and recommendations as appropriate. For selected study participants, a tentative appointment was made at this time to equip the individual's own, personal vehicle with the instrumentation package to be used for the remaining data collection activity.

Instrumented Vehicle Comparison of Independent Driving and a Driving Evaluation

The instrumented vehicle portion of the study was designed to acquire 2-3 hours of additional time, location, and driving speed data, obtained over a period of up to one week, for each of five study participants (two males, three females). These individuals did not receive any additional compensation for this activity. This was an exploratory effort, essentially a "proof of concept" that (older) individuals would allow the installation of unobtrusive recording equipment in their own vehicles, and that an instrument package sufficient to the present data needs could be affordably integrated from off-the-shelf electronics and would work reliably – without intervention or maintenance – for an extended period.

The instrumentation package included the same components identified earlier – a video recorder box (under seat) and two-camera enclosure (mounted on windshield under the insider

rearview mirror), plus the “car chip” plugged into the OBD2 port to sample vehicle speed once every second. A GPS unit was also placed inside the camera box. As before, a 12V adapter plugged into the cigarette lighter powered these devices, using a motion sensitive switch to ensure that they were in operation only when the vehicle was driven to protect the battery. Connecting cables were tucked under molding, carpet, etc., in participants' vehicles. The cost of each instrument package was under $800, and it required approximately 30 minutes to install and test the components for use in an individual's private car.

As noted earlier, the goal in this data collection activity was to permit a comparison of an (older) driver's behavior when he/she is driving in a test vehicle, with an evaluator, to that same individual's behavior and habits when driving in the same milieu in his/her own vehicle, without an evaluator in the car. To that end, the five study participants were asked to drive according to their normal habits and patterns while their cars were instrumented, with the understanding that such driving could but was not required to include roads in common with the test route they had driven on during their evaluations with the OT/CDRS.

After five to seven days, by appointment, the instrumentation was removed from each participant's car and was returned to TransAnalytics' offices, to offload speed (car chip), location (GPS), and video data for later analysis. An inspection of each participant’s vehicle was conducted to ensure that no damage had resulted from the installation of the instrument package.

DATA ANALYSIS

Two sets of analyses were conducted in this study. The **primary** analyses, which included the entire sample of older drivers taking known *potentially drive- impairing* medications, were designed to reveal the extent to which driver characteristics—including medication usage—could account for categorical differences in (1) an on-road driving evaluation based on scores assigned by an Occupation Therapist/ Certified Driver Rehabilitation Specialist (OT/CDRS); (2) objective measures of brake reaction time (BRT); and (3) functional status measures using a computer-based battery of tests validated as significant predictors of at-fault crash risk in previous NHTSA research. These were between-subjects analyses.

Secondary analyses were performed for the subset of the study sample for whom an instrumentation package was installed in their personal vehicles for a week to unobtrusively monitor their driving habits. These analyses examined differences in attentional behavior—operationally defined as glance direction—as a function of the level of demand of the road/traffic situation, when an individual was driving independently in his/her own car compared to during the on-road evaluation with the OT/CDRS. These analyses relied heavily on the video recordings of the driver’s face and the external roadway scene, and entailed an extensive data reduction/coding effort, described below. The secondary analyses were focused on within-subject differences.

Primary Analyses: Effects of Driver Characteristics/Medications

Analysis technique. A total of 21 analyses spanning three different types of dependent measures are described below. These explored the relationships between medication usage and/or other characteristics that distinguish the older drivers in the test sample, and the behaviors used as outcome measures in this research. Outcomes included measures of driving performance and driver functioning, which were scored in terms of broad, categorical differences between study participants. Certain measures (e.g., driving evaluation scores) were recorded only as categorical data; while other measures (brake reaction time) that were initially recorded as continuous data were re-coded as categories of performance. This approach may be justified both in terms of the exploratory nature of this research, and the prolific number of combinations of medications examined herein coupled with the modest effect that can be expected for any particular types of drugs among a group of generally healthy, active seniors. The goal in each analysis was to identify the combination of medications (and/or other driver characteristics) that could best separate study participants according to the classifications of behavior used for a given outcome variable. A linear modeling approach, Logistic Regression, was chosen for these analyses.

Independent/predictor variables. The driver characteristics of greatest interest in these analyses were the prescription drugs, both PDI and non-PDI medications, plus over-the-counter drugs taken by the study participants. All medications identified during the pharmacist reviews were logged according to their *therapeutic class*, not their brand or generic name. In some cases multiple *subclasses* of drugs—though directed at a common therapeutic intervention (e.g., to control high blood pressure)—were distinguished by their metabolic or pharmacological action. These are shown in Table 10 and Table 11.

Other driver characteristics aside from medication usage serving as independent/ predictor variables in these analyses included driver age (years); gender; residence (CCRC) location; the study participant's level of familiarity with the driving evaluation route; and the frequency of exposure to all or part of the driving evaluation route in his/her everyday travel. The latter were integer ratings, from "1" to "7" on a bipolar scale where "1" was the lowest score (least familiar; least often traveled) and "7" was the highest score (most familiar; most often traveled).

Initially, all 72 of the medication classes and subclasses shown in Tables 10 and 11 were included in the present analyses. For every entry in these tables, a "0" or a "1" was entered in each study participant's data file to denote whether s/he was or was not using the medication in question. However, an initial run using PROC LOGISTIC in SAS revealed a number of problems with this analysis approach. Usage data for eight medications was constant; it was necessary to discard these from the model, as things that do not vary cannot be useful predictors. The data for 23 other predictors was completely collinear — that is, these values were totally predicted by some linear combination of other variables in the model. These problems were addressed by combining drugs with related therapeutic applications into a reduced number – 16 – of categories, to allow entry of the medication usage data into the present analyses. This classification scheme is apparent in Appendix E,

Table 10. Classes and subclasses of prescription drugs represented in the study sample.

Drug Class and Subclass	Drug Class and Subclass
Antihypertensive Alpha 1 Adrenergic Blocker Beta Blocker ACE Inhibitor Calcium Channel Blocker Combo Calcium Channel Blocker – ACE Inhibitor Angiotensin II Receptor Antagonist Loop Diuretics Potassium Sparing Diuretic Thiazide Diuretic Combination Diuretic	Antidiabetic Sulfonylurea Biguanide Alpha Glucosidase Inhibitor Thiazolidine Dipeptidyl peptidase 4 Osteoporosis Calcitonin Hormone Bisphosphonate Cholesterol Lowering HMG-COA Reductase Inhibitor Antilipemic
Antidepressants SSRI SNRI	Antianxiety Benzodiazepine Anti-Anxiety Non-BZD
Asthma Beta Adrenergic Agents Inhaled Steroid	Nasal Spray Antihistamine Anticholinergic Steroid
Anticoagulant (Coumadin Type)	Immunomodulator
Antiarrhthmic	Antibiotic
5 Alpha Reductase Inhibitor	Antihistamines - Non Sedating
Antipsychotic	Corticosteroid
Anti Mania	Phosphodiesterase 5 Enzyme Inhibitor
Anti Convulsant	Thyroid Supplement
Aromatase Inhibitor	Potassium Supplement
Cholinesterase Inhibitor	Selective Estrogen Receptive Modulator
Dopamine Agonist	Hormone Replacement Topical Cream
CNS Stimulant	Topical Antibiotic
Proton Pump Inhibitor	Glaucoma Drops
Antispasmodics GU	Steroid Eye Drops
NSAID	Opiate Agonist

Table 11. Classes and subclasses of OTC medications represented in the study sample.

Drug Class and Subclass	Drug Class and Subclass
OTC Analgesic	OTC Antacid
OTC Antihistamine (Sedating)	OTC H2 Blocker
OTC Analgesic Antihistamine (Combination)	OTC Cough Drops
OTC Topical Analgesic	OTC Vitamin/Mineral
OTC Antiplatelet	OTC Laxative
OTC/Joint Supplement	OTC Saline Nasal Spray
OTC Eye Tears	OTC/Fish Oil Supplement
OTC/Eye Supplement	OTC Antiflatulant
OTC/Herbal	OTC Antifungal Topical

which identifies the specific PDI and non-PDI drugs taken by all participants as per the pharmacist review and as per self-report to the OT/CDRS just prior to their driving evaluations. The drug classifications only (i.e., used as analysis variables) are listed below:

- Antihypertensive diuretic
- Antihypertensive non-diuretic
- Anti-platelet/anticoagulant
- Anti-diabetic
- Neurologic
- Osteoporosis
- Gastric acid secretion reducer
- Cholesterol lowering
- Anti-spasmodics GU
- Non-steroidal anti-inflammatory drugs (NSAID)
- Antidepressants/antianxiety
- PDI eye preparations
- Sedating antihistamines
- Vitamins/minerals/supplements
- PDI other
- Non-PDI other

Dependent/criterion variables. Three broad criterion variables were selected for the primary analyses: *driving evaluation, brake response,* and *functional status*. For the planned analyses, a varying number of specific measures of interest were identified in each of these areas, each containing a specified number of data levels or categories. As noted earlier, these analyses were designed to test the ability of the regression model to sort study participants into categories of performance based on medication usage and other driver characteristics.

The measures selected for analysis under *driving evaluation* are identified below, with the outcomes categorized as indicated. All outcomes reflected scores assigned by the OT/CDRS, using the form referenced earlier (also see appendix D). A separate analysis was planned for each of the following measures:

- Overall rating of driving competence: four categories
  1 = Concerns about driving
  2 = Fair driver/ lacks numerous good driving habits
  3 = Adequate driver/few potential problems
  4 = Good driver/no concerns
- General driving errors: two categories
  1 = Safety is compromised: inconsistent performance; single error or pattern of errors
  2 = Safety is not compromised: consistent performance, only minor errors; skills are adequate (but a comment may be added as a qualifier)
- Controlled intersection driving errors: two categories *(same as above)*
- Uncontrolled intersection errors: two categories *(same as above)*
- Turns errors: two categories *(same as above)*
- Visual skills errors: two categories *(same as above)*

- Evaluator intervention: two categories
  1 = dual brake and/or steering intervention by evaluator required
  2 = no brake or steering intervention by evaluator required

For *brake response*, two behaviors were selected for analysis: the number of errors on the "alerted" trials—where the subject responded to the alerting stimulus instead of to the target stimulus—and the reaction time on the un-alerted trials. For the former measure, there were three alerted trials presented to each subject, so the range of possible scores (response categories) for number of errors was 0 to 3. These data were categorized as follows:

- Response errors/alerted trials: four categories
  1 = 0 errors
  2 = 1 error
  3 = 2 errors
  4 = 3 errors

For the latter measure, the raw brake reaction time (BRT), in milliseconds, was calculated as the mean of the three un-alerted trials presented to each subject; these means were then sorted into quartiles. The raw, un-alerted BRT means for the 44 field study participants, ranged from 0.653 s to 4.315 s. The categories selected for analysis are indicated below:

- BRT quartiles/unalerted trials: four categories
  1 = 0.653 s to 0.877 s
  2 = 0.877 s to 1.065 s
  3 = 1.065 s to 1.356 s
  4 = 1.356 s to 4.315 s

For the remaining criterion variable, *functional status*, the measures selected for analysis included two measures of physical ability (leg strength/general mobility and head/neck flexibility); two measures of visual ability (static visual acuity, at high and low contrast); and four measures of cognitive ability (working memory, visual search with divided attention, visuospatial ability/visual closure, and visual information processing speed with divided attention). Categories of performance were assigned for each measure using cut points defined during the NHTSA research project, *Model Driver Screening and Evaluation Program*; also see Staplin, Gish, and Wagner (2003). These are indicated below:

- Head/neck flexibility: two categories – level of apparent deficit
  0 = no deficit (pass)
  1 = deficit present (fail)
- Leg strength/general mobility: three categories – level of apparent deficit
  1 = no deficit
  2 = mild deficit
  3 = serious deficit
- Acuity/high contrast: three categories *(same as above)*
- Acuity/low contrast: three3 categories *(same as above)*
- Working memory: three categories *(same as above)*
- Visuospatial ability/visual closure: three categories *(same as above)*

- Information processing speed, with divided attention: three categories *(same as above)*
- Visual search, with divided attention: three categories *(same as above)*

Preliminary runs using PROC LOGISTIC revealed additional problems associated with the selection of criterion variables as outlined above. Some of these variables have very few (one or two) individuals populating a given category level. This indicated a need both to reduce the overall number of outcomes examined in the analyses, and to further consolidate data into fewer categories for each of the remaining variables, to increase cell sizes.

These problems were addressed by selecting only four outcome measures – two *driving evaluation* measures and one each for *brake response* and *functional status* – for a revised analysis approach that could potentially allow a successful fit to the regression model. In addition, performance was recoded into only two categories for each measure, as follows.

- **Analysis 1**. This analysis of the overall OT/CDRS rating of driving competence seeks to predict which individuals received scores of 1 or 2 (fair driver, with numerous bad habits *or* OT has definite concerns) versus 3 or 4 (good driver, no concerns *or* adequate driver with only a few potential problems).
- **Analysis 2**. This analysis retains the "evaluator intervention" variable from the previous list, seeking to predict which study participants' behavior did versus did not elicit an intervention of *any kind* by the OT/CDRS.
- **Analysis 3**. This analysis of brake response time seeks to predict only which study participants scored in the top half (quartiles 1 *or* 2, as specified earlier) versus the bottom half (quartiles 3 *or* 4) of the BRT distribution, for the "unalerted" trials.
- **Analysis 4**. This analysis focuses on the four cognitive measures (the last four items in the list above), seeking to predict which study participants scored in the "no deficit" *or* "mild deficit" ranges versus the "serious deficit" range for any of these functional status indicators.

Secondary Analyses: Behavioral Variability Within Subjects

A secondary set of analyses explored differences in a measure of driver attention – moment-to-moment gaze direction – as a function of road and traffic conditions, for specified maneuvers, for independent driving versus the formal (OT/CDRS) driving evaluation carried out in this research, for a selected sub-sample of older drivers. An additional case study analysis contrasted speed choice by a single subject on identical roads, traversed alone (personal vehicle) and with the OT/CDRS. The following analyses used data obtained via the in-vehicle instrumentation package.

The first analysis required the two-camera (driver's face and forward road scene) video to be coded in terms of four elements: glance, infrastructure, traffic, and maneuver. These elements, in turn, were each defined in terms of a set of mutually exclusive attributes, as listed below. More extensive descriptions for coding attributes are provided in Appendix F.

GLANCE: straight ahead through the windshield;
right only;
left only;
right+up (inside mirror);
down+ inside (dashboard, radio, etc.);
over shoulder (left or right).

INFRASTRUCTURE: continuous, unbroken section of roadway;
stop-controlled intersection;
signalized intersection;
intersection with channelization for merge/yield— driver in turn lane;
school or pedestrian crossing;
at-grade rail crossing;
parking lot or garage.

TRAFFIC: no threat of any conflicts with other traffic;
car following only—same or adjacent lane (rear-end crash potential);
opposing traffic only (head-on or angle crash potential);
car following and opposing traffic.

MANEUVER: same path moving forward;
driver turns left;
driver turns right;
driver changes lanes (right or left);
driver overtakes/passes another vehicle;
backing/reverse movement;
driver's vehicle is stopped/no movement.

For each of the four elements above, one attribute was coded for every frame of video recorded in the independent drives and OT/CDRS driving evaluations, at 12 frames of video per second (12 Hz). In other words, subjects' data files included an entry for glance, infra-structure, traffic, and maneuver approximately every 1/8 of a second. The software tool used for this data coding task was Anvil (Kipp, 2001). The interface used for video data coding is displayed in Figure 9, showing each attribute value for the selected frame.

The coding of "behavior in context" from continuous, in-car video, as described above, provides data sufficient to address a large number of research questions relating to driver adaptation/compensation to varying traffic/demand conditions, in addition to providing heretofore scarce evidence of (older) drivers' actual (i.e., instead of self-reported) exposure patterns. Given the limited scope of this pilot investigation, two questions of particular interest to this research team were framed for the present analyses:

Figure 9. Software interface for coding attributes from driver face (top) and road camera (bottom) continuous video.

(1) *"Across all traffic, infrastructure, and maneuver attribute values excluding "car following only," "parking lot or garage," and "driver's vehicle stopped/no movement," respectively, how does drivers' glance behavior correlate between independent driving in their own vehicles and their driving evaluations with the OT/CDRS?"*

(2) *"For the specific scenario when an (older) driver is negotiating a signalized intersection – approaching and then continuing through without turning – what is the correlation in glance behavior between independent driving and driving with the OT/CDRS, under the same traffic (demand) conditions."*

The former correlation was calculated using pooled data from the five drivers in the sub-sample, to offer an overall comparison between the two modes (independent driving versus driving evaluation). Virtually all aspects of road geometry, traffic operations, and driving maneuvers are included in this comparison. The latter correlation was calculated for only the selected video frames associated with codes denoting a "forward moving" maneuver, at a "signalized intersection," for matched traffic conditions.

In both cases, these correlations were based on the number of video frames where the included drivers were looking straight ahead, versus to the left, right, down/inside vehicle, up/right at the inside rearview mirror, or over their shoulder, for their independent drives versus their OT/CDRS driving evaluations, for just those frames where the driver was moving, on a public street or highway, and not in a car-following mode.

In the second, "case study" analysis, the correspondence between one subject's speed choice during independent travel compared to her OT/CDRS driving evaluation, for travel over identical sections of road, at roughly the same time of day, was examined. The date/time/place match between the two drives was based on GPS data, as were the speeds examined in this analysis.

It may be noted that the obtained match in driving locations for this subject was fortuitous; her independent driving while the on-board instrumentation package was installed was not scripted or directed in any way by the research team. Also, the reader should understand that this was a purely descriptive exercise, based on data analyzed for a single subject; its purpose was to explore the feasibility and utility of this approach for future investigations of within-subject variability in driving habits.

PILOT TEST RESULTS

Data Summary

Descriptive statistics reporting key sample characteristics follow. The composition of the study sample by age, gender, and location (residential community) is indicated in Table 12. As indicated, study participants ranged in age from 57 to 89, with a mean of 78.82 and median of 80. The sample was composed of 18 (41%) males and 26 (59%) females. Twenty-four, or 55%

of the sample, were residents at the Cokesbury Village CCRC, while 20 (or 45%) were from the Erickson residential communities.

Table 12. Composition of study sample.

Sample Characteristic	Cokesbury	Erickson	Overall
Number of Participants	24	20	44
Males/Females	12/12	6/14	18/26
Age Range	57-89	68-86	57-89
Mean Age	78.6	79.1	78.8
Median Age	80	82	80

An overview of the medication classes and subclasses used by study participants, in the aggregate, was presented earlier in Tables 10 and 11. A graphical summary of the number of classes of PDI and non-PDI drugs used by study participants according to their “brown bag” medication review with the visiting pharmacist review is presented in Figure 10; these same counts of PDI and non-PDI drugs according to study participants’ self-reports on the day of their driving evaluations are displayed in Figure 11. As indicated, the number of medication (classes) that could potentially influence driving performance (or functional status) measures were fewer than the number identified in each individual’s pharmacological inventory. For a comprehensive, person-level tabulation of the PDI and non-PDI drugs identified during the pharmacist reviews, and as taken on the day of each individual's driving evaluation, see Appendix E.

The correlation of study participants’ ages with the number of PDI medications they reported on the day of their driving evaluations was calculated. The result was $r = 0.09$ (n.s.).

The request that study participants obtain letters/printouts listing their prescription medications from their pharmacists yielded very few responses; and those few could be incomplete, to the extent that individuals stated that they obtained medications from multiple sources. Thus, one clear-cut result in this work is the demonstrated superiority of the "brown bag" method to acquire information about the medication usage of (older) drivers. It is also important to note, however, that while a "brown bag" review may produce a complete inventory of the drugs in an individual's possession, some or many may be taken on an “as needed” basis, so studies attempting to relate the use of specific drugs or combinations of drugs to driving performance must query medication use at the time of testing.

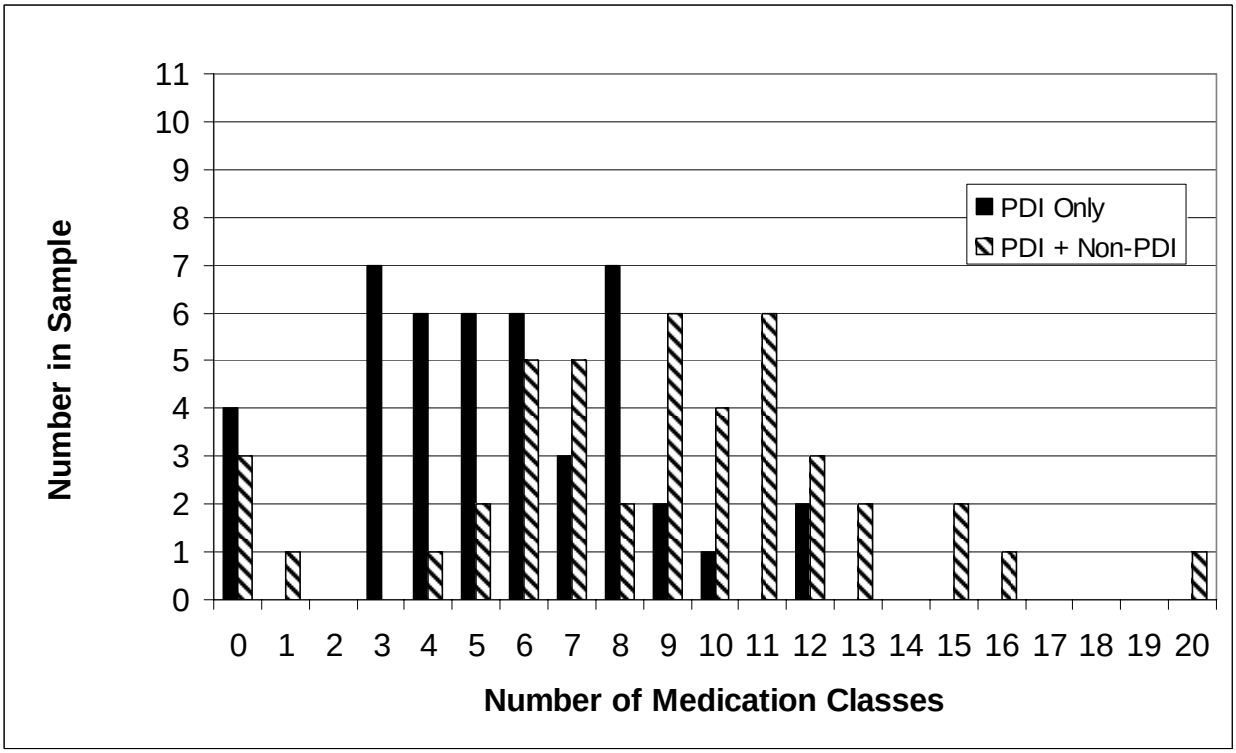

Figure 10. PDI and non-PDI medication usage by research sample: pharmacist review.

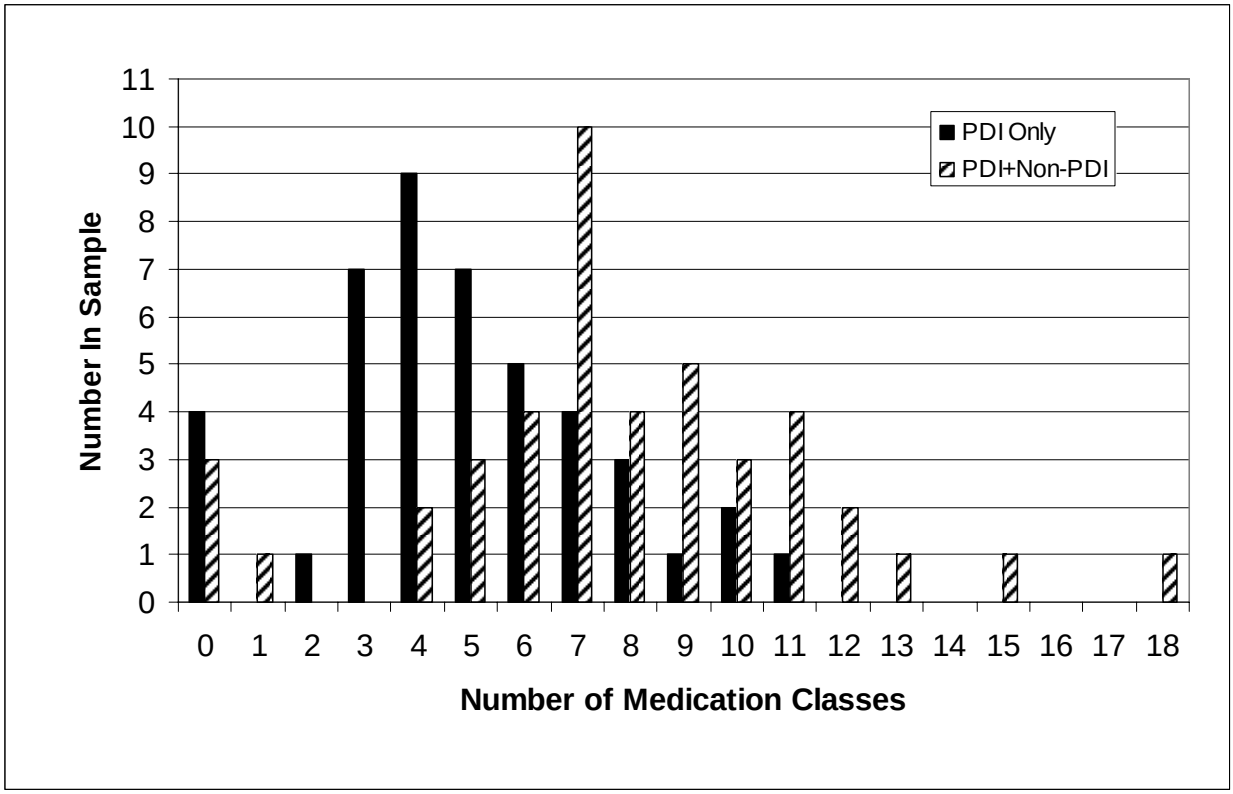

Figure 11. PDI and non-PDI medication usage by research sample: self-report before driving evaluation.

The results for the driving performance measures obtained for this research sample are summarized in Table 13. Both the subjective (OT/CDRS ratings) and objective (un-alerted brake response time) data were categorized into four levels for analysis, as described earlier. Table 13 indicates the number and percent of study participants at each performance level, for the overall driving evaluation ratings. As shown, only 8 of 44 study participants were scored by the OT/CDRS at level 1 ("concerns about driving") or level 2 ("lacks numerous good driving habits"). This table also shows that the mean response time even for the slowest quartile of study participants, 1.87 sec, falls well within the "design driver" *perception-response time* of 2.5 sec used by the highway engineering community. However, while these trials are labeled "un-alerted," they represent data from an experiment where an evaluator was riding with the respondent, and so may not be compared directly with "surprise" conditions when a person driving independently, in traffic, must react to an unexpected object/threat in their path.

Table 13. Data summary for subjective and objective driving performance measures.

Measure	N	Performance level (number and percent of sample)			
		1 (worst)	2	3	4 (best)
OT/CDRS evaluation: overall rating	44	4	4	20	16
Brake response time: un-alerted trials	44	Performance level (mean RT by quartile, in seconds)			
		1 (slowest)	2	3	4 (fastest)
		1.87	1.20	0.94	0.75

The results of the computer-based measures of functional abilities for the present research sample are displayed in Table 14. Forty study participants completed these measures; data are missing for four individuals due to equipment/software problems. Table 14 shows the number and percent of the sample for who *no* deficit, a *mild* deficit, or a *serious* deficit was indicated by the screening protocol, for each measure. Inspection of these results

Table 14. Functional status of study participants, by screening measure.

Measure	N	Functional Status (Number and Percent of Sample)		
		No deficit	Mild deficit	Serious deficit
Acuity/high contrast	40	38 (95%)	1 (2.5%)	1 (2.5%)
Acuity/low contrast	39	35 (90%)	3 (8%)	1 (2%)
Leg strength/mobility	40	34 (85%)	5 (13%)	1 (2%)
Head/neck mobility	40	17 (43%)	--	23 (58%)
Visuospatial ability/ visual closure	40	26 (65%)	8 (20%)	6 (15%)
Visual search/divided attention	40	10 (25%)	27 (68%)	3 (7%)
Working memory	40	27 (68%)	7 (17%)	6 (15%)
Information processing speed/divided attention	40	25 (63%)	6 (15%)	9 (22%)

reveals that, as expected, only a minority of the research sample appeared to have a serious deficit on any given measure. An exception was shown for the "head/neck flexibility" measure, which has also been associated with an elevated failure rate in the Maryland pilot older driver study (Staplin et al., 2003). It is uncertain whether this reflects a methodological artifact or a genuine prevalence level of stiff/arthritic neck and upper torso conditions among this cohort.

In Table 15, additional detail is provided to show the number of study participants, average age of participants, and the average number of both the medication classes and PDI-medication classes—according to both the pharmacist review and as reported on the day of their driving evaluation—for all who scored in the "no deficit," "mild deficit," and "serious deficit" category on each functional test.

Table 15. Functional status by participant's age and medication use.

Deficit Level	Number of Subjects	Average Age	Pharmacist Review: Average Number of Medication Classes	Pharmacist Review: Average Number of PDI Medication Classes	Self-Report Before Driving Evaluation: Average Number of Medication Classes	Self-Report Before Driving Evaluation: Average Number of PDI Medication Classes
Measure: Acuity/high contrast						
No Deficit	38	78.4	8.79	5.48	7.74	4.87
Mild Deficit	1	85	8	5	8	5
Serious Deficit	1	81	9	4	7	4
Measure: Acuity/low contrast						
No Deficit	35	78.03	8.74	5.4	7.66	4.83
Mild Deficit	3	84.67	9	6.33	8.33	5.67
Serious Deficit	1	81	9	4	7	4
Measure: Leg strength/mobility						
No Deficit	34	78.3	9.09	5.59	7.94	4.97
Mild Deficit	5	82.6	5.8	3.2	5.2	3
Serious Deficit	1	69	13	10	13	10
Measure: Head/neck mobility						
No Deficit	17	77.1	8.88	5.65	7.94	5.24
Serious Deficit	23	79.8	8.69	5.22	7.57	4.56
Measure: Visuospatial ability/visual closure						
No Deficit	26	79.7	7.65	4.66	7	4.31
Mild Deficit	8	76.3	9.75	6.63	8.25	5.88
Serious Deficit	6	77.3	12.33	7.0	10.17	5.83
Measure: Visual search/divided attention						
No Deficit	10	76.5	8.6	5.2	7.5	4.5
Mild Deficit	27	79.2	8.41	5.26	7.48	4.85
Serious Deficit	3	80.7	12.67	7.33	10.67	6.0
Measure: Working memory						
No Deficit	27	76.7	9.67	6.04	8.67	5.52
Mild Deficit	7	81.9	7.85	4.71	6.0	3.71
Serious Deficit	6	83.3	5.83	3.33	5.5	3.17
Measure: Visual information processing speed/divided attention						
No Deficit	25	78.9	8.36	5.04	4.6	7.32
Mild Deficit	6	79.2	9.83	5.83	5.5	8.83
Serious Deficit	9	77.6	9.22	6.11	5.11	8.11

These results indicate that poorer performance (greater deficit) was not always associated with increasing age, nor with increasing medication usage. These mixed findings are highlighted in the results for the measures of cognitive function, which are both the strongest crash predictors, and are those for which a relationship with medication usage might logically seem most likely. Specifically, the data for visuospatial ability and processing speed show no direct relationship with age, and only a weak relationship is evident for the visual search measure. The incidence of a serious deficit in working memory with increasing age is more pronounced, however. At the same time, there is a general trend toward greater deficits with increasing medication usage for three of four measures of cognitive ability; but for the memory measure there is an inverse relationship: those who manifested *greater* memory deficits were taking *fewer* drugs, overall, and fewer PDI drugs as well.

These results underscore the importance of (1) individual measures to determine functional (cognitive) status, rather than using chronological age as a proxy; and (2) looking beyond simply the number of drugs a person is taking when examining the potential associations between medication usage, age, and driving performance. A more detailed data summary for specific combinations of variables of interest follows. These include tabulations, presented graphically in Appendix G, of the *age x medication* profiles for study participants who are further classified according to (1) driving evaluation rating (four levels), (2) brake response time (four levels), and (3) evidence of cognitive deficit (3 levels), respectively.

Looking first at the age-by-drug profiles for performance, as scored by the OT/CDRS, only 4 participants "failed" the driving evaluation. The age range of these participants was 83 to 88, and the number of PDI medications ranged from 4 to 8. Moving to the color-coded profile for medication class by un-alerted brake response time quartile, the 11 participants who scored the poorest ranged in age from 76 to 89, with the majority (82%) 83 or older. The number of PDI medications for these 11 participants ranged from 0 to 8. Finally, the drug profile color-coded to denote levels of cognitive deficit (none, mild, or serious) shows subjects with serious cognitive deficits ranging in age from 68 to 88, and taking medications in 0 to 11 PDI drug classes. It appears that neither age nor number of PDI medications can adequately explain performance on these outcome measures.

One potential explanation for the small number of participants who failed the driving evaluation according to the OT/CDRS, compared to the number of participants with serious cognitive deficits, is that the demands of the test route were not high enough to elicit driving errors commensurate with the cognitive deficits suggested by the functional screening measures. It is interesting to note that the subset of failing older drivers (as scored by the OT/CDRS) is also the oldest. This may be explained by the fact that PDI medications are more impairing to driving performance for the oldest participants due to the way the aging liver metabolizes medications, and other physiological changes that occur with aging, i.e., 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 (Herrlinger and Klotz, 2001). Still, it should be noted that study participants who appear to have one or more serious cognitive deficits (denoted by red shading in the third graphic in Appendix G) include individuals in each decade from 68 to 88.

Part of the difficulty in detecting any pattern of changes in performance with changes in drug profiles is the strong overlap in the pharmacopeia of the research sample due to the inclusion criteria for the study. Participants were initially recruited on the basis of taking an ACE inhibitor to control hypertension, plus another PDI medication from one of three other classes (gastric acid secretion reducers, antidepressants, or cholesterol-lowering drugs). These criteria were subsequently relaxed to allow people taking any antihypertensive plus another PDI medication to participate. The result was that a large majority of study participants were taking antihypertensive medications (39 of the 44 were taking non-diuretic antihypertensive medications, and 23 were taking diuretic antihypertensive medications); and nearly as many (36 of 44) were taking cholesterol-lowering medications.

Despite this artifact of the selection strategy for study recruitment, the data relating age and medication class to driving performance, as summarized in the first graphic in Appendix G, may deserve a closer look – in particular, the entries for ACE Inhibitors. ACE Inhibitors (e.g., Lisinopril, Accupril, Altace) decrease the activity of angiotensin and as a result, blood vessels dilate and blood pressure is reduced. LeRoy and Morse (2005) found that drivers taking ACE inhibitors experienced a motor vehicle crash rate that was 23% greater (OR=1.23) than that of drivers not taking these medications. Dizziness, drowsiness, excessive tiredness, weakness, and lightheadedness are potential side effects that could impair safe driving performance. In this context, it may be noteworthy that 75% of the sample who "failed" the OT evaluation in the present study were taking an ACE inhibitor, compared to 50% who received a rating of "fair," 35% who received a rating of "adequate," and 25% who received a rating of "good." A similar pattern was not observed in the graphic summarizing the (categorical) performance on the unalerted brake response time task, where 36% of both the best- performing and worst-performing participants were taking this medication. However, when considering the apparent level of cognitive deficit indicated by the included screening measures, 37% of those with a serious deficit and 36% of those with a mild deficit were taking ACE inhibitors, compared to only 14% of those without any apparent deficits. Thus, a pattern may be broadly discerned in this sample, whereby ACE inhibitors are associated with poorer outcomes on multiple safety surrogates.

At a still finer level, the combination of ACE inhibitors and thiazide diuretics appears potentially problematic. Side effects of thiazide diuretics include hypotension and dizziness. This combination may cause synergistic effects, increasing the risk of hypotension (abnormally low blood pressure) and leading to lightheaded, dizziness, and even fainting and seizures, if blood pressure becomes too low. The age-by-medication profiles depicted in Appendix G reveal that, of those "failing" the OT/CDRS driving evaluation, 25% (1 of 4) were taking this combination on the day of their evaluation, as were 25% (1 in 4) of those who scored "fair." This compares to 10% (2 of 20) of those scored as "adequate," and only 6% (1 in 16) of those scored as "good" on their driving evaluations. At the same time, 18% of those in the worst-performing quartile on the brake response time task were taking this combination, compared to 9% in the best-performing quartile. And, study participants without any apparent cognitive deficits were free of the ACE inhibitor/thiazide diuretic combination, while 14% of those with a mild deficit and 5% of those with a serious deficit were using these two drugs together.

These preliminary observations about possible driver-impairing effects of multiple medication usage are placed in context by scholarly reviews of the relationship between age and human drug metabolism (Herrlinger & Klotz, 2001; Schmucker, 2001; and Kinirons & O'Mahony, 2004). All of these authors conclude that although some measures of drug metabolism are diminished in the elderly, this population is characterized by significant inter-individual variability in drug metabolism, drug action, and adverse reactions. Certainly, the tentative results described above do not in any way diminish the importance of individual assessment of the ability to drive safely.

Logistic Regression

Four separate stepwise logistic regression analyses were performed using SAS, one for each of the following classification outcome variables:

- Cognitive status – seeking to predict which study participants scored in the "no deficit" *or* "mild deficit" ranges versus the "serious deficit" range for any of the included functional ability measures in this domain.
- OT intervention – seeking to predict which study participants' behavior did versus did not elicit an intervention by the OT/CDRS.
- Brake response time – seeking to predict which study participants scored in the top half (quartiles 1 *or* 2) versus the bottom half (quartiles 3 *or* 4) of the BRT distribution, for the "un-alerted" trials.
- Driver evaluation – seeking to predict which individuals received scores of 1 or 2 (fair driver, with numerous bad habits *or* OT has definite concerns) versus 3 or 4 (good driver, no concerns *or* adequate driver with only a few potential problems).

The analysis of effects statistics for each regression model appears below.

Analysis of effects for cognitive status

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Antidepressants_Anti	1	0.0042	0.9485
Antidiabetic	1	2.9847	0.0841
AntihypertensiveDiur	1	0.0092	0.9237
AntihypertensiveNonD	1	0.0381	0.8451
AntiPlatelet_Anticoa	1	0.0166	0.8976
Antispasmodics_GU	1	0.0468	0.8288
CholesterolLowering	1	0.0353	0.8509
GastricAcidSecretion	1	0.7668	0.3812
Neurologic	1	0.0130	0.9091
NSAIDs	1	0.0758	0.7831
Osteoporosis	1	0.1564	0.6925
PDIEyePreparations	1	0.2963	0.5862
PDIOther	1	1.7715	0.1832
SedatingAntihistamin	1	1.6977	0.1926

Analysis of effects for OT intervention

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Antidepressants_Anti	1	0.0254	0.8733
Antidiabetic	1	0.0080	0.9288
AntihypertensiveDiur	1	0.0148	0.9032
AntihypertensiveNonD	1	0.0044	0.9469
AntiPlatelet_Anticoa	1	0.0093	0.9230
Antispasmodics_GU	1	0.0006	0.9806
CholesterolLowering	1	0.0005	0.9815
GastricAcidSecretion	1	0.0251	0.8742
Neurologic	1	0.0032	0.9551
NSAIDs	1	0.0161	0.8991
Osteoporosis	1	0.0170	0.8961
PDIEyePreparations	1	0.0071	0.9330
PDIOther	1	0.0116	0.9142
SedatingAntihistamin	1	0.0009	0.9762

Analysis of effects for brake response time

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Antidepressants_Anti	1	0.0141	0.9055
Antidiabetic	1	1.0865	0.2973
AntihypertensiveDiur	1	1.1426	0.2851
AntihypertensiveNonD	1	0.0161	0.8991
AntiPlatelet_Anticoa	1	0.6569	0.4177
Antispasmodics_GU	1	0.0134	0.9079
CholesterolLowering	1	0.0175	0.8949
GastricAcidSecretion	1	0.1689	0.6811
Neurologic	1	0.0023	0.9616
NSAIDs	1	0.4581	0.4985
Osteoporosis	1	2.4712	0.1159
PDIEyePreparations	1	1.2059	0.2721
PDIOther	1	1.7511	0.1857
SedatingAntihistamin	1	0.2780	0.5980

Analysis of effects for driver evaluation

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
Antidepressants_Anti	1	0.0586	0.8088
Antidiabetic	1	0.0176	0.8946
AntihypertensiveDiur	1	0.0086	0.9262
AntihypertensiveNonD	1	0.0052	0.9422
AntiPlatelet_Anticoa	1	0.0118	0.9134
Antispasmodics_GU	1	0.0525	0.8188
GastricAcidSecretion	1	0.0589	0.8082
Neurologic	1	0.0252	0.8739
NSAIDs	1	0.0211	0.8845
Osteoporosis	1	0.0125	0.9109
PDIEyePreparations	1	0.0025	0.9604
PDIOther	1	0.0191	0.8901

For each analysis, SAS used maximum likelihood estimates to order the predictors. The criterion for predictor entry into the model (SLENTRY) and predictor retention in the model (SLSTAY) were set close to 1 so that the full model could be obtained. Variables were entered in order from highest to lowest model effect size.

A significant Wald Chi-Square indicates that a predictor's regression coefficient is not equal to zero. The maximum likelihood estimates are compared to the proposed estimate (either 1 or 0 with a binary outcome, as in the present analyses) and are divided by the variance in the parameter estimate. The result is then compared to the normal distribution. The square of the difference is compared to the chi-square distribution, yielding an X^2 probability value as shown above. As indicated, *there are no significant effects among these analyses.*

With specific reference to the driver evaluation results, it may be noted that the predictor "Cholesterol Lowering" never reached the SLENTRY criterion for inclusion in the model, and the predictor "Sedating Antihistamine" was removed because it did not meet the SLSTAY criterion for retention in the model.

The absence of statistically significant drug effects for any of the outcome variables in these analyses may reflect several different factors. First, a larger sample is clearly needed to analyze the effects of classes of drugs - and especially specific drugs - on performance. Next, the consenting participants in this study may not be representative of older drivers. Based on unsolicited comments from rehabilitation services staff it is not only possible, but likely, that the "poorest" drivers would not volunteer for such a study. In addition, if drivers have been taking their medications for a long time, it is possible that they have learned ways to compensate for the

effects that the drug has on their driving performance. Finally, the influence of other drugs – alcohol, in particular – is an unknown but possibly potent covariate that could explain individual differences in drug metabolism.

Instrumented Vehicle Results and Case Study

The first analysis examining variability in driving behavior for a sub-sample of five study participants, comparing their independent driving to their driving during the evaluation with the OT/CDRS, measured the correlation in glance distribution across nearly all included traffic, infrastructure, and maneuver conditions. The second analysis examined the same correlation for a particular situation of interest: intersection negotiation.

Both of these analyses relied on the coding of driver behavior from video data recorded in the test vehicle and in participants' own cars. Specifically, the software tool (Anvil) was used to assign attribute values for glance location, infrastructure, traffic condition, and maneuver, for every frame of video, at 12 frames per second. Two video coders contributed to this task. To evaluate inter-rater reliability, glance location was scored independently, by both coders, in a test clip of slightly under 3 minutes. The results appear in Table 16.

Table 16. Inter-rater reliability summary table.

Rater	Glance Location	Frame Count	Percent
1	0	1578	77.9
1	1	61	3.0
1	2	63	3.1
1	3	300	14.8
1	4	0	0.0
1	5	24	1.2
2	0	1581	78.0
2	1	92	4.5
2	2	50	2.5
2	3	218	10.8
2	4	0	0.0
2	5	85	4.2
Correlation between raters: all locations, aggregate video			0.99
Correlation between raters: all locations except forward, aggregate video			0.93
Correlation between raters: frame by frame			0.77
Coefficient of determination (r-squared): frame by frame			0.60

As shown in this table, across all glance locations, for all video frames (i.e., in the aggregate), a very high correlation (0.99) was found. Because the driver was looking forward in most frames, and this was the easiest behavior to code, a separate correlation for glances away

from the forward direction was also calculated; this was slightly lower but still impressive at 0.93. Of greatest interest was the consistency between raters on a frame-by-frame basis. This correlation fell to 0.77, due principally – based on a review of discrepant frames – to differences of a few frames in the perceived onset and offset of changes in glance direction by one coder versus another. These values, being in line with the reliability levels reported in a closely-related study on driver distraction using continuous video coded from a driver face camera (Stutts et al., 2003), were deemed satisfactory to support the planned analyses of behavioral variability in the independent drives versus driving evaluations.

Beginning with an examination of virtually all driving done by this sub-sample – excluding from video analysis only those frames where they were stopped, were following another vehicle, or were in a parking lot – there are modest differences in the proportion and distribution of glances away from the forward direction during independent driving versus the driving evaluations. With reference to Table 17, these study participants' behavior was marked by a substantial increase in the amount of time they were looking down/inside their vehicles, coupled with fewer glances to the inside rearview mirror (Right+Up location), during independent driving. Of course, traffic conditions were not identical; but the independent driving videos selected for this comparison were matched for road type and time of day/visibility condition with each individual's driving evaluation. Tentatively, then, this observed variability in driver behavior may be associated at least in part with the circumstances of the evaluation itself.

The correlation in overall glance distribution is almost perfect, due to the overwhelming percent of the time drivers are (appropriately) looking forward. Excluding the frames with a forward glance location, the correlation falls to 0.58; further, this change appears to be localized to a few specific differences in glance behavior. In particular, the differences associated with independent driving suggest a greater willingness to divide attention, engaging in secondary tasks and/or sampling information from inside the vehicle (e.g., radio controls) at the expense of sampling mirror information. These differences, while certainly not surprising, point to a degree of vigilance and self-monitoring to exclude distracting behavior during a formal driving evaluation, that individuals probably will not manifest in their everyday driving.

Table 17. Glance location for five participants during driving evaluations and independent driving, for all scenarios except parking lots, stopped vehicle, and car following.

Glance Location	Driving Evaluation		Independent Driving	
	Count	Percent	Count	Percent
Forward	6113	84.93%	4845	82.54%
Right+Up	363	5.04%	206	3.51%
Right Only	288	4.00%	377	6.42%
Left Only	349	4.85%	219	3.73%
Down+Inside	26	0.36%	178	3.03%
Over shoulder	59	0.82%	45	0.77%
N =	7198		5870	
Correlation all 6 glance locations	0.998583			
Correlation excluding forward	0.580994			

Next, this comparative analysis of the present surrogate for attention (glance distribution) was performed for a much more restrictive set of conditions—only when the driver approaches and continues straight through a signalized intersection as a lead or isolated vehicle, i.e., not in car following mode. This situation was selected for special examination because of the demands to actively and continuously search for potential conflicts with other road users while sampling signal status, other regulatory information, and formal and informal guidance cues in the environment; and because a considerable body of research has highlighted older drivers' errors leading to crashes at intersections as a preeminent safety concern. These results are presented in Table 18.

As shown in this table, the correlation for overall glance behavior remains very high, but when frames showing a forward glance are excluded the correlation falls to 0.24. This relatively weak correspondence may be explained by more glances down and inside the vehicle, coupled with fewer glances toward the inside rearview mirror and the complete elimination of over-the-shoulder glances during the independent drives. There was also a shift toward more "right only" and fewer "left only" glances during independent driving.

Again, it must be noted that while the video selected for this comparison was recorded during similar operating conditions, variability in traffic conditions and other factors during the driving evaluations versus the independent drives was inevitable. Such differences in, for example, the geometries of the particular intersections traversed by these study participants could account for the absence of over-the-shoulder glances. It is less obvious, however, why drivers continuing straight through the intersection would devote less attention searching to the left versus to the right during independent driving, given the nearly equal distribution of glances to the left and right at intersections during their driving evaluations. And the apparently greater willingness of study participants to devote attention to locations inside the vehicle during intersection negotiation – though still a small percentage of their overall glance distributions – highlights a difference between independent driving and (older) individuals' behavior during a driving evaluation that may have significant safety implications.

Table 18. Glance location for five participants during driving evaluations and independent driving, for intersection negotiation only.

Glance Location	Driving Evaluation		Independent Driving	
	Count	Percent	Count	Percent
Forward	644	79.31%	539	79.03%
Right+Up	55	6.77%	25	3.67%
Right Only	43	5.30%	76	11.14%
Left Only	37	4.56%	11	1.61%
Down+Inside	8	0.99%	31	4.55%
Over shoulder	25	3.08%	0	0.00%
N =	812		682	
Correlation all 6 glance locations	0.992106			
Correlation excludes forward	0.235991			

The comparative analysis with the closest congruence between independent driving and driving during the OT/CDRS evaluation was a "case study" carried out in the Hockessin, DE, vicinity for a selected research participant. Based on GPS data recorded with the in-vehicle instrumentation, the routes traversed by individual during the driving evaluation have been traced with a thin yellow line in Figure 12. Overlaid on the yellow line are thicker lines in red, blue, turquoise, and amber, which denote the routes this person traversed on four separate independent drives. With reference to this figure, some or all of each of these independent drives shares common road segments – presenting the same operational and infrastructure elements to drivers – with the driving evaluation route.

It is possible that this individual had other exposure during independent driving on route segments in common with the driving evaluation. However, there was a cell phone tower in the area that interfered with GPS reception, resulting in intermittent signal loss during independent driving. The available GPS recordings permitted location matches that are accurate to two significant digits for latitude and longitude coordinates, corresponding to a resolution of approximately 60 feet.

A database was created containing 318 records among the four independent drives, with coordinates that matched those on the driving evaluation route. For each location identified via matching coordinates, the driver's speed was examined. The number of matched locations where speed choice was higher and lower during independent driving, versus during the driving evaluation was tabulated. In addition, an average speed was calculated for all locations on each of the four independent drives where speed was higher, and where it was lower, than the same individual's speed on the same road segments during the driving evaluation. These results are presented in Table 19.

As indicated, this study participant drove faster at nearly all of the matched locations on the "red segment" during the driving evaluation, compared to independent driving, and at substantially more locations on the "blue segment" as well. In contrast, speed choice was higher during independent driving on the "turquoise segment," and even more so on the "amber segment." In fact, it is on the "amber segment" where the study participant's speed choice was higher during independent driving for the largest proportion of matched locations; and, this road segment has the lowest traffic volume – and so the driver's speed choice is least likely to be affected by other motorists – than on any of the other common road segments.

Table 19. Differential speed choice (mph) by one participant during the driving evaluation versus independent driving, on four common road segments.

Common Road Segment	Higher Speed Choice During Driving Evaluation			Higher Speed Choice During Independent Driving		
	Mean speed: driving evaluation	Mean speed: independent driving	Matched locations in database	Mean speed: driving evaluation	Mean speed: independent driving	Matched locations in database
Red segment	38.3	30.8	86	26.8	27.8	2
Blue segment	40.7	32.6	87	26.7	36.9	50
Turquoise segment	29.4	24.6	22	23	25	40
Amber segment	22.7	20.2	8	23.2	31.1	22

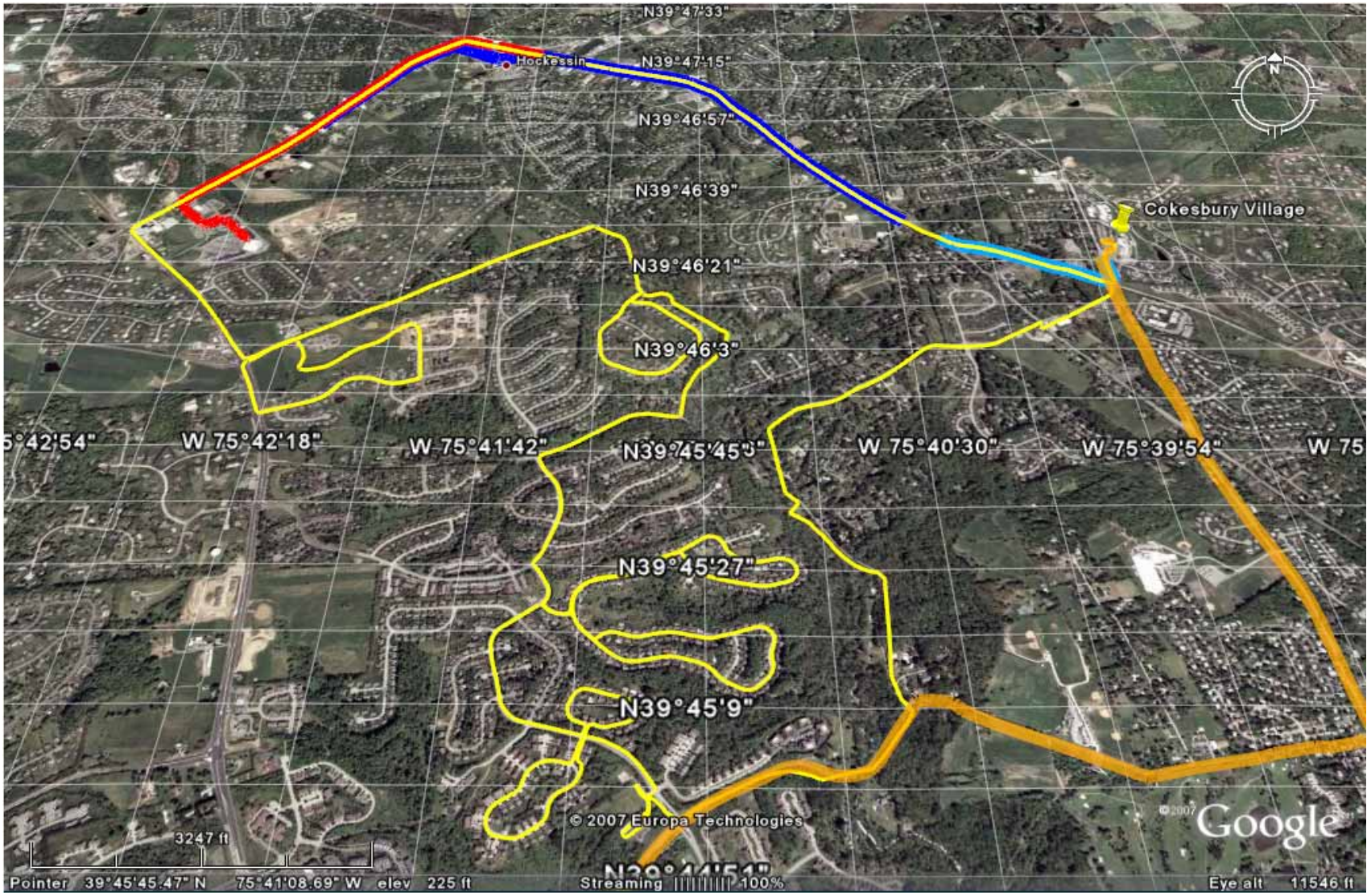

Figure 12. Map showing common road segments (shaded red, blue, turquoise, and amber) for the independent drives and the driving evaluation.

Recent Reports, Studies, and National Surveys on Polypharmacy and Driving

Overview and Objective

The purpose of this project task was to review all relevant technical literature published since the previous NHTSA report in this subject area.[1] This chapter contains summaries of recently published research on medication usage, injury data, and/or other relevant variables that could potentially impact the relationship between PDI medications and driving, that were posted in the SafetyLit database between October 2005 and October 2007. SafetyLit is a free service of the Center for Injury Prevention Policy and Practice at San Diego State University in collaboration with the World Health Organization. The weekly SafetyLit update provides abstracts of English language reports from researchers in 35 disciplines relevant to preventing unintentional injuries, violence, and self-harm. SafetyLit staff and volunteers regularly examine more than 2,600 scholarly journals from many nations, and also review conference proceedings and reports from government agencies and organizations. SafetyLit summaries are drawn from anthropology, economics, education, engineering specialties, ergonomics, law and law enforcement, medicine, physiology, psychology, public health, public safety, nursing, social work, traffic safety, and other fields.

Included in this chapter is an update on drug prevalence in fatal and non-fatal injury motor vehicle crashes. Studies are summarized providing new information about the effects of specific drugs/drug classes on driving, including an anti-seizure medication (topiramate) for migraine prevention and other therapies; acute and stable dosing of opioids; sedating and non-sedating antihistamines; antidepressants; short and long half-life sedative-hypnotics; an immediate-release versus extended-release anti-anxiety medication (benzodiazepine); a skeletal muscle relaxant (carisoprodol); and anti-diabetic medications. The chapter concludes with an examination of studies bearing on the risk of falling associated with chronic medical conditions versus the effects of the medications that treat these conditions.

PREVALENCE OF MEDICATIONS AND DRIVING

Schwilke, Sampaoi dos Santos, and Logan (2006) reported on patterns of drug (illicit and therapeutic) and alcohol use in fatally injured drivers in Washington State between 2001 and 2002. These data were obtained for 370 drivers who died within 4 hours of a traffic crash. Driver culpability for the crash was not provided in the data that were analyzed; therefore drug use rates by crash-causing versus non-causing drivers could not be determined. The sample included 277 men ranging in age from 15 to 87 with a mean age of 38, and 93 women 16 to 91 with a mean age of 47.

[1] Literature Review, Lococo, K.H., and Staplin, L. "Polypharmacy and Older Drivers: Identifying Strategies to Study Drug Usage and Driving Functioning Among Older Drivers." Contract DTNH22-02-D-85121, Report DOT HS 810681. Washington, DC: National Highway Traffic Safety Administration. Available on the Web at http://www.nhtsa.gov/staticfiles/DOT/NHTSA/Traffic%20Injury%20Control/Articles/Associated%20Files/Polypharmacy.pdf.

Of the 370 cases tested, 150 blood samples were positive for alcohol. Of the 150 cases positive for alcohol, 63 (42%) were positive for one or more impairing drugs. For the most frequently identified drugs, the rate of drug and combined alcohol use included: cannabinoids (53%), cocaine (38%), methamphetamine (33%), diazepam (53%), and diphenhydramine (50%). Without considering alcohol, rates of drivers testing positive for drugs included the following: cannabinoids (12.7%), amphetamines (4.86), benzodiazepines (5.14%), cocaine/met (4.86%), diphenhydramine (2.7%), hydrocodone (1.89%), phenytoin (1.89%), morphine (1.62%), and amitriptyline (1.08%). The significance of the combined alcohol and drug use in this population is that the magnitude of impairing drug use by drivers may be underestimated because of the procedures used in DUI enforcement. Investigations of impairing agents in traffic stops typically end with a positive blood or alcohol result. These data suggest that individuals with impairing amounts of alcohol in their systems may more often have impairing drugs in their systems than is documented, which could have contributed to their driving impairment. The study authors note that if the patterns of drug and alcohol use in the sample population carry over into the general impaired driving population, as many as 40% of all individuals arrested for alcohol-related driving offenses could be at least partially under the influence of drugs.

The rate of benzodiazepines may be underestimated because clonazepam and lorazepam (two drugs with known effects on driving) are not detected by the autopsy blood test procedures, and would have gone undetected in the study population. The two most frequently detected benzodiazepines were diazepam (detected in 15 cases) and nordiazepam (detected in 7 cases). Midazolam was detected in 4 cases. The concentrations detected suggested therapeutic use. In these drivers, alcohol was detected in 54% of the diazepam-positive cases, 43% of the nordiazepam-positive cases, and 50% of the midazolam-positive cases.

Poly-drug use in this population was common, and often included a combination of illicit and prescription drugs. For the alcohol-free cases, 9.5% tested positive for two or more impairing drugs.

Kaplan, Kraner, and Paulozzi (2006) analyzed the prevalence alcohol and drug use in 458 drivers who were fatally injured in crashes between 2004 and 2005 in West Virginia. The West Virginia Office of the Chief Medical Examiner routinely screens all victims of motor vehicle crashes for evidence of impairment from alcohol, licit, and illicit drugs. This includes narcotics (e.g., heroin and opioid analgesics), marijuana, stimulants (e.g., cocaine and amphetamines), depressants (e.g., benzodiazepines and barbiturates), and other licit drugs (e.g., antidepressants and antihistamines). Up to three drugs may be listed in the database used for the analysis (Fatality Analysis Reporting System [FARS]), and if multiple drugs are found, they are recorded in the following order: narcotics, depressants, stimulants, marijuana, and other licit drugs. Drugs administered by emergency medical services are not included. Fifty percent of the drivers who were fatally injured had alcohol or drugs in their bodies, and 12.2% had both. Alcohol was detected in 33.8% of the deceased drivers. Detectable levels of at least one drug type were reported for 28.4% of the decedents, and two or more types of drugs in 9% of the deceased drivers. Opioid analgesics were present in 7.9%, depressants in 7.9%, stimulants in 4.4%, marijuana in 8.5%, and other licit drugs such as antidepressants and antihistamines in 9.4%. The three most common opioid analgesics were hydrocodone (2.8% of the fatally injured drivers testing positive for drugs), oxycodone (2.0%), and methadone (1.5%). The depressants were

sedatives, including benzodiazepines (6.6%) and barbiturates (6.6%), and the muscle relaxant meprobamate/carisoprodol (0.6%). The most common benzodiazepines were diazepam and alprazolam. Cocaine was the most frequently identified stimulant (4.4%). A limitation of the research findings is that the FARS data do not describe the degree of intoxication, whether the drugs were used recreationally or therapeutically, or whether the user was an acute or stable user of a drug (e.g., level of familiarity). The database also does not assign driver fault, so some of the impaired drivers may not have been responsible for their crashes, and some impaired drivers who survived crashes but killed other road users are not included.

Kurzthaler et al. (2005) investigated the prevalence of benzodiazepines and alcohol (alone and together) in 1,611 non-fatally injured patients admitted to the emergency room at the University Hospital of Trauma Surgery in Innsbruck, Austria, between January 1 and December 31, 1995. In their sample, injuries were the result of a traffic crash for 269 patients. For the full sample of 1,611 patients, those 60 or younger tested positive for alcohol, as well as for benzodiazepines in combination with alcohol more often than patients over 60. All benzodiazepine concentrations were within the therapeutic range or lower. Almost all blood samples positive for benzodiazepines were traced to diazepam. Concentrating only on the sample of patients who were involved in traffic crashes, 7.1% tested positive for benzodiazepines; the mean diazepam plasma level was 87 $\pm$ 64 ng/L. This suggested that benzodiazepine use was associated with therapeutic use, rather than abuse of these drugs. In this same sample of 269 patients, 29.4% tested positive for alcohol; the mean blood alcohol concentration was 1.53 $\pm$ 0.54 g/l, which is above the legal limit in Austria at the time of the investigation (0.8 g/l). The percent of the traffic-crash sample testing positive for both alcohol and benzodiazepines was 1.9%.

Ch'ng et al. (2007) analyzed blood samples taken from 436 drivers injured in crashes in Victoria, Australia, and who were transported to a trauma center for care following the collision. The objective of the analysis was to examine the use of commonly abused drugs (amphetamines, benzodiazepines, opiates such as morphine and codeine) as well as cannabis and cocaine among drivers injured in motor vehicle crashes. Drivers who received opiates or benzodiazepines for treatment at the trauma center were eliminated from the analysis. The finding of particular interest to the present research is that benzodiazepines were found in 15.6% of the drivers across all age groups, but the use of benzodiazepines increased with age, and was highest among women drivers 65 and older. Four of the 13 women 65 and older (31%) tested positive for benzodiazepines.

Effects on Driving of Specific Drugs/Drug Classes

Topiramate (an anti-epileptic also used in migraine revention and other therapies)

Topiramate (Topamax) is a seizure disorder treatment that received additional FDA approval for prevention of migraine headaches in August 2004, and is being prescribed for off-label uses such as psychiatric disorders (e.g., schizophrenia and bi-polar disorder); eating disorders (e.g., bulimia, binge eating, obesity, and anorexia nervosa); as an adjunct therapy to treat weight gain associated with olanzapine, SSRIs, and other anti-psychotic medications; neuropathic pain; and alcohol and drug dependency (Gordon & Logan, 2006). Its potentially driver impairing side effects include sedation; dizziness; confusion; difficulty concentrating;

shaky and unsteady body movements; rapid and repetitious involuntary eye movements; decreased visual acuity; hypoglycemia leading to loss of consciousness; and tingling or numbness in the arms and legs. The manufacturer states that patients should be warned about the potential side effects and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental, motor, or visual performance.

In forensic toxicology investigations of topiramate-positive drivers reported by Gordon and Logan (2006), psychomotor impairment was evident with blood concentrations within normal therapeutic range. As an example, a 31-year-old female was prescribed topiramate for an eating disorder. She drove off the highway and crashed into the median. Responding officers noted thick slurred speech, heavy eyelids and dilated pupils. She had a lack of coordination and could not stand unassisted and was arrested for DUI. Topiramate at therapeutic levels (8.1 mg/L) was identified in her blood as well as lorazepam at 0.01 mg/L. In the case of a 50-year-old female driver who was involved in a no-damage, non-injury collision, the driver was observed with severe lane drift, hitting curbs, and almost driving onto a sidewalk where children were playing. The only drug found in her blood was topiramate at a concentration of 14.2 mg/L. Gordon and Logan note that as anti-epileptic medications are increasingly used to treat psychiatric disorders, their prevalence in impaired driving cases has increased. Between 1998 and 2004, 68 suspected impaired drivers tested positive for topiramate in Washington State. The mean and median age of the drivers testing positive for the drug was 42. The majority (68%) of the cases were female. The median blood topiramate concentration was 6.4 mg/L (mean 8.4 mg/L, range 1-180 mg/L, sd 6.4). Alcohol was detected on only 5 of the 68 arrested drivers.

Opioids

New (Acute) Opioid Dosing. Verster, Veldhuijzen, and Volkerts (2006) compared driving performance, laboratory test performance, mood changes, and subjective measures of alertness for 18 healthy subjects who participated in a randomized, double-blind, placebo-controlled crossover study. Treatment sequences were randomized across the participants, and test days were separated by a wash-out period of seven days. Subjects were given the following medications/dosages: bromfenac 25 mg; bromfenac 50 mg; oxycodone/paracetamol 5/325 mg; oxycodone/paracetamol 10/650 mg; and placebo.

Bromfenac (Duract) is a non-steroidal anti-inflammatory drug that was indicated for short-term management of acute pain. Because it was pulled from the market during the data collection phase as a result of potentially serious side effects (liver damage), this summary will be limited to the results of the opioid drug (oxycodone) on subjects' performance. Oxycodone is an opioid agonist that is often prescribed in combination with paracetamol to reduce the opioid dosage while retaining the analgesic efficacy, to reduce opioid-related adverse effects. The recommended dosage is 5 mg oxycodone with 325 mg paracetamol.

Subjects were given a treatment dose or a placebo 30 minutes prior to a standardized breakfast. One hour after dosing, a standardized on-road driving test was given. The 100-km road test was conducted in a dual-controlled vehicle on a two-lane road. Subjects were instructed to maintain constant speed of 90 km/h (56 mph). Outcome variables included a measure of

weaving (standard deviation of lateral positioning, or SDLP); and standard deviation of speed. The laboratory tests were given 2.5 hours after administration of the medications or the placebo, and included a Sternberg memory scanning test, a tracking task, and a divided attention task. Subjective assessments of their own driving performance following the drive test as well as the level of effort required to perform the test were obtained, in addition to subjective assessments of alertness level.

Drive test results showed no significant differences between the opioid treatments and the placebo; however, there was a significant difference in SDLP between the high dose (23 cm) and the low dose (20.5 cm) of the opioid medication. The difference between the high dose and the placebo (+1.9 cm) was not significant, and is less than that observed with blood alcohol concentrations of .05 grams per deciliter. There were also no significant differences between the opioid treatments and the placebo on any of the laboratory tests, although performance was worse under both opioid treatment conditions than the placebo condition.

Significant differences between the placebo and the opioid treatment were evident in the driving-related subjective assessments, the subjective assessment of alertness, and the mood change assessment. Level of mental effort invested in the driving task was assessed on a scale that ranged from "absolutely no effort" to "extreme effort," with consecutive sublevels including "almost no effort," a little effort," "some effort," "rather much effort," "considerable effort," "great effort," and "very great effort." Compared to the placebo, mental effort during driving was significantly elevated after the high dose of the opioid, but not after the low dose of the drug. Also, a significant dose-response relationship on mental effort was found for the opioid drug. The authors suggest that the lack of impairment on the drive test may have been related to the participants reporting increased effort during driving while under the influence of this drug. Alertness was assessed on a 21-point, equal-interval scale. Compared to the placebo, alertness was significantly decreased for both doses of the opioid, and there was also a significant dose-response relationship. Mood changes were assessed by the Addiction Research Center Inventory (ARCI_-49) Questionnaire. This questionnaire uses 49 yes/no questions that relate to five scales, differentiating between mood changes induced by psychoactive drugs. The five scales are: euphoria, dysphoria, sedation, intellectual efficacy and energy, and activation. After the drive test, sedation was significantly increased in the high-dose opioid condition, as was dysphoria.[2] There was a significant dose-response relationship for the opioid drugs on the dysphoria scores.

Stable Opioid Dosing. Byas-Smith, Chapman, Reed, and Cotsonis (2005) compared driving performance (on-road and closed course) and laboratory tests of attention and visual information processing for 50 normal volunteers with no pain, 11 opioid-free patients with chronic pain, and 21 patients who had chronic pain and were taking opiates. The most frequently used opioid analgesic was oxycodone. Of the 32 patients, only 2 used an opioid analgesic alone. Morphine equivalent daily opioid doses averaged 118 mg (median 40 mg).

Subjects participated in a community drive test in their own vehicles over 7 miles of urban residential driving and 4 miles of highway driving. The test administrator followed in another car and filmed the participant's car. The recorded videotape was used to identify driving

[2] Characterized as a state of feeling unwell or unhappy, *Merriam-Webster Medical Dictionary*, 2007-2008. See http://medical.merriam-webster.com/medical/dysphoria.

errors (speeding, turning, stopping, and lane violations). The closed course consisted of five stations including a 50-yard straight course for driving forward; a 20-yard straight course for reverse driving; a 100-yard slalom course with frequent S-shaped turns; a circular-shaped course demanding constant turns; and parallel parking. The course was delimited with multiple, 3-foot tall, orange rubber cones. Test administrators positioned near the course recorded three measures: time to complete the station, number of touches of a cone by the automobile, and number of cones run over or knocked down.

Laboratory tests included the Test of Variables of Attention (TOVA) and the Digit Symbol Substitution Test (DSST).

Results of the community drive tests indicated no driving errors besides speeding for any groups; 90% of subjects in each group exceeded the speed limit by at least 5 mph, but none greater than 15 mph. There were no significant differences among groups on speeding. Results of the five stations of the obstacle course drive showed no significant group mean differences for total time, number of cones impacted or knocked down. There were also no group differences in accuracy of parking. To evaluate the effect of different doses of opioids on driving performance, the opioid group was divided into two subgroups: 16 patients taking more than 20 mg of morphine equivalent per day and those taking less than or equal to 20 mg per day. A comparison of these two subgroups found differences in only one analysis—patients in the higher dose group completed the circle course significantly faster than those in the lower dose group.

The laboratory tests showed no significant differences between groups on the TOVA. On the DSST, the healthy volunteers showed significantly higher scores, with no significant differences between the opioid and non-opioid patient groups. Group differences disappeared however, when age and years of education were controlled for.

The study authors state that these findings provide direct evidence that at least a subset of patients with chronic pain on a stable opioid analgesic regimen are capable of operating a motor vehicle safely during daytime, good-weather conditions. Given that there were no significant differences on the dependent measures between the opioid-treated patients with chronic pain, the opioid-free patients with chronic pain, and the healthy volunteers, Byas-Smith et al. (2005) indicate that an absolute prohibition against driving while taking opioid medications for pain control is contraindicated by the study findings.

Similar conclusions were drawn from a study of the effects of long-term treatment with controlled release oxycodone (CRO) using a computerized test battery (Gaertner, Radbruch, Giesecke, Gerbershagen, Petzke, Ostgathe, Elsner, & Sabatowski, 2006). The objective of the study was to demonstrate that patients treated with CRO did not perform significantly worse in the tests than the untreated controls. The test battery measured attention reaction, visual orientation, motor coordination, and vigilance. Performance of the patients treated with CRO was compared to that of the control sample, in addition to transformation of the control subjects' data equivalent to performance under the influence of .05 g/dL blood alcohol (from a prior study). The alcohol-impaired control data were used to define clinically significant impairment. Therefore, to show non-inferiority in test performance of opioid patients compared to controls, CRO patient performance would need to be significantly better that that of the control group with

a blood alcohol concentration of .05. Performance of 30 patients suffering from non-cancer pain and treated with CRO for at least four weeks (and without a dose change in the prior 12 days) was compared to the performance of 90 controls, with three age-matched controls for each patient. Age ranged from 25 to 77. The average dosage of CRO was 76 mg/day (range 20 to 280 mg). The mean current pain intensity of the CRO patients was 4.8 on an 11-point scale where 0 = no pain and 11 = pain as severe as possible.

Combining the cognitive items of the battery, the CRO patients performed better than the age-independent control group with a blood alcohol level of .05, but the difference was not statistically significant. This result cannot demonstrate that CRO treatment is not un-impairing. The researchers also looked at the percentage of patients in the CRO and control group (not under the influence of alcohol) who passed the single tests in the test battery, acknowledging that this was a weaker statistical analysis, albeit one that is recommended by German legislation. In Germany, test batteries similar to the one used in the study are employed for "traffic delinquents" who are denied permission to drive if one or more of the tests is failed (i.e., a test result is below the 16^{th} percentile of the age-independent reference range). The control group patients passed an average of 4.1 of the 5 tests, while the CRO patients performed only slightly worse, passing a mean of 4.0 tests. The difference in the percentage passing from the control group and the CRO group was not significant. The percentage of patients passing all 5 tests was 56% for the control group and 39% for the CRO group; this difference also was not significant. The daily oxycodone dosage correlated moderately (r=0.45, p-.01) with the number of wrong answers on the reaction time under pressure test. In addition, there was a moderate inverse relationship between dosage and the vigilance test score. The authors concluded that stable treatment with CRO in chronic non-cancer patients does not prohibit driving, however individual assessment is necessary.

Antihistamines

Tashiro et al. (2005) conducted a study to determine whether cellular phone use while driving further degrades the performance of drivers using antihistamines (both sedating and non-sedating). In a randomized, double-blind, placebo-controlled, three-way crossover study, healthy volunteers received fexofenadine HC1 120 mg (a non-sedating antihistamine), hydroxyzine HC1 30 mg (a non-benzodiazepine anoxiolytic/hypnotic, also used as a sedating antihistamine), and a placebo. Subjects were 18 male volunteers age 20 to 26. Brake reaction time while driving on a controlled course consisting of two straight lines 1.5 km in length connected by u-shaped turning roads at both ends, served as the dependent measure; 25 trials under each condition were performed. Subjective assessments of sedation (Stanford sleepiness scale and the line analog rating scale) were also provided. For each drug or placebo condition, the following four driving conditions were conducted: (1) driving only; (2) driving while answering simple arithmetic questions on the cellular phone; (3) driving while answering complex arithmetic questions on the phone; and (4) driving while engaged in conversation on the cellular phone, where the subject was asked to provide 1- to 2-minute answers on six to eight pre-determined topics.

Both assessment tests of subjective sleepiness showed that subjects given hydroxyzine were significantly less alert/more sedated than those who were administered fexofenadine or the placebo. There were no significant differences in subjective alertness/sleepiness between fexofenadine and the placebo groups.

Brake reaction time (BRT) showed significant differences as a result of drug administered and driving condition as follows. For the driving only condition, there were no significant differences in BRT as a function of the drug type (or placebo) given. For each of the three conditions where subjects used a cell phone, those driving under the influence of hydroxyzine had significantly slower BRTs that those taking either fexofenadine or the placebo: there were no significant differences in BRT for the fexofenadine and placebo groups.

The BRT of hydroxyzine vs. placebo was compared under the four driving conditions. Subjects who were administered the placebo and were engaged in discussions of simple calculations had slower BRTs than subjects administered hydroxyzine but were not using their cell phone at all. When the hydroxyzine subjects were engaged in discussions of simple calculations, their BRTs were slower than the BRTs of the placebo group engaged in discussions of simple calculations.

Similarly, subjects given the placebo and were engaged in discussions of complex calculations had slower BRTs than subjects given hydroxyzine and not talking on their cell phone at all. BRTs of the placebo group performing complex calculations were not significantly different from BRTs of the hydroxyzine group completing the simple calculations.

Subjects given the placebo and who were engaged in general conversations on their cell phones had significantly slower BRTs than the hydroxyzine-treated subjects who were not using their cell phone, but significantly faster BRTs that the hydroxyzine-treated subjects who were engaged in general conversations on their cell phone.

Comparisons of BRT for fexofenadine versus placebo under the four driving conditions showed that for any driving condition where they were using their cell phones, placebo-treated subjects had slower BRTS than the fexofenadine-treated group who were not using cell phones. But no differences were shown as the result of the placebo versus the fexofenadine administration, when both groups were performing either of the three tasks while using their cell phones.

This study's findings are consistent with other research on the effects of fexofenadine (a non-sedating antihistamine) on driving performance, and furthers the state of the knowledge that fexofenadine does not impair driving performance even in the presence of divided attention tasks. Hydroxyzine, on the other hand (a sedating antihistamine) was associated with significantly greater sedation, and significantly slower BRTs when subjects were performing divided attention tasks. Thus, drivers given hydroxyzine will be slower at recognizing potential hazards or threats in the traffic situation ahead, and slower to apply their brake to stop or slow the vehicle as needed. Anything that divides their attention from the main task of driving (such as cell phone use) will exacerbate the risk of crashing. Although older drivers were not included in the sample, the negative effects of the sedating antihistamine on driving performance would likely be magnified, as would the combined effect of the antihistamine and the divided attention task.

Antidepressants

Brunnauer, Laux, Geiger, Soyka, and Moller (2006) evaluated the fitness to drive of 100 depressive inpatients on clinically relevant doses of various antidepressants (by antidepressant class). Inclusion criteria included antidepressant monotherapy, steady-state pharmacologic conditions (all patients were considered for discharge in at least three days), and possession of a valid driver's license. Mean age was 46.8 (sd = 13.6). Forty patients received tricyclic antidepressants (TCAs: amitriptyline, doxepin, maprotiline, or trimipramine), 25 received selective serotonin reuptake inhibitors (SSRIs: citalopram or paroxetine), 20 received a noradrenergic and specific serotonergic antidepressant (NaSSA: mirtazapine), and 15 received a serotonin-norepinephrine reuptake inhibitor (SNRI: venlafaxine). Subjects with a history of neurologic illness, substance abuse, or mental retardation were excluded. Fitness to drive was measured according to German guidelines for road and traffic safety using a computerized test battery that assesses the following domains: visual perception, selective attention, vigilance, and reactivity and stress tolerance. Sixteen percent of the depressive patients were considered unfit to drive (labeled as "severely impaired" and failing in more than 40% of test parameters) and 60% were considered "moderately impaired" (failed in less than 40% of test parameters) and in need of individual assessments of their ability to drive. Only 24% of the patients passed the test according to German guidelines for driving (i.e., not more than 1 standard deviation below the mean of normative data in psychomotor domains). Looking at the global driving score, 10% of the patients taking TCAs passed the tests without impairments, as did 20% of those treated with venlafaxine, 28% treated with SSRIs, and 50% treated with mirtazapine. Comparisons between mirtazapine and each of the other antidepressants were statistically significant, indicating better performance with mirtazapine. On the psychomotor and visual perception tests, depressed patients taking TCAs were more impaired than those treated with SSRIs or mirtazapine. There were no significant differences in performance between patients treated with TCAs and venlafaxine. Subjects treated with mirtazapine showed significantly better performance on tests measuring reactivity and stress tolerance than those treated with TCSs, SSRIs, or venlafaxine. In the selective attention test, patients treated with SSRIs and mirtazapine performed significantly better than those treated with TCAs and venlafaxine.

It should be noted that all patients treated with mirtazapine were under steady-state pharmacologic conditions and received their doses in the evening (the night before testing). This is important because earlier studies on healthy subjects given mirtazapine as a daytime dose showed impairments in driving ability (Wingen, Bothmer, Langer et al., 2005; Rideout, Meadows, Johnsen, et al., 2003). In this study, depressive patients given mirtazapine in the evening performed better than patients in other groups, and greater percentages passed the driving test criteria for licensure. The findings indicate that antidepressant therapy affects fitness to drive differently in depressed patients, and physicians should be aware of this and conduct individual counseling for depressed patients wishing to drive.

Sedative-Hypnotics

Staner et al. (2005) investigated the driving abilities of patients diagnosed with primary insomnia, after repeated dosing of sedative hypnotic drugs. Single and repeated (7-day) doses of zolpidem (10 mg), zopiclone (7.5 mg), lormetazepam (1 mg) or a placebo were administered in a

crossover design to 32 patients. Lormetazepam is a benzodiazepine not approved for sale in the United States or Canada, but is one of the most prescribed benzodiazepine hypnotics in France, where the study was conducted. Zolpidem (also known as "Ambien") is a strong hypnotic drug that has no significant muscle relaxant, anxiolytic, or anticonvulsant activity when administered at a clinically relevant dose, and zopiclone is an effective hypnotic that induces weaker myorelaxation than benzodiazepines. The average half-life of lormetazepam is 10 hours, compared to 5 hours for zopiclone, and 1.9 hours for zolpidem. Treatments were administered at bedtime from day 1 to day 7, and its effect was assessed at the beginning (day 2) and at the end (day 8) of each treatment period after a night spent in the sleep laboratory.

Driving simulator tests took place 9 to 11 hours post-dose. Driving simulation with EEG monitoring was conducted on a FAROS driving simulator with a roadway display video projection system that subtended a 120-degree visual field. It had no movement capabilities. Subjects "drove" for 60 minutes along the simulated highway during daytime; in light traffic; with occasional long, wide curves; and repetitive landscaping. The program calculated mean, median, and standard deviation of absolute speed, of deviation from the speed limit, of deviation from the ideal route, and the number of collisions (with other vehicles or crash barriers).

Results showed significantly poorer performance on the driving simulation measures of deviation of absolute speed and deviation from the speed limit for patients taking lormetazepam, compared to the placebo. Patients taking zopiclone had significantly more collisions than patients taking the placebo. Zolpidem had no effect on the driving performance measures. Both the lormetazepam and zopiclone had significant next-day effects (9 to 11 hours post dosages) on EEG correlates of vigilance level (benzodiazepine-like alterations in beta and alpha power), a phenomenon referred to as "pharmacological dissociation." Zolpidem did not alter next-day physiological EEG rhythms 9 to 11 hours post-dose. The authors suggest that the poor driving performance associated with lormetazepam and zopiclone was related to their prolonged CNS effects during the driving simulation test. The residual effects of the hypnotics increased with increases in their half-life. Zolpidem had the shortest half-life (1.9 hours), followed by zopiclone (5 hours) and by lormetazepam (10 hours).

Anti-Anxiety Medications

Leufkens, Vermeeren, Smink, van Ruitenbeek, and Ramaekers (2007) compared the effects of extended-release (XR) and immediate-release (IR) alprazolam on the on-road driving performance of 18 healthy volunteers age 20 to 45. Citing Isbister, O'Regan, Sibbritt, and White (2004) and others, Leufkens et al. state that alprazolam (e.g., Xanax) is the most frequently used benzodiazepine for the treatment of panic disorder and anxiety. Alprazolam IR has a half-life ranging from 10 to 18 hours, and a peak blood plasma concentration is reached within 0.7 to 1.8 hours after ingestion. Patients report side effects including drowsiness, dizziness, and reduced alertness. Alprazolam XR was developed to reduce the adverse side effects associated with alprazolam IR. Its peak plasma concentrations are approximately half those of alprazolam IR and they occur between 5 and 12 hours after ingestion.

As a requirement for participation in the study, subjects were prohibited from using any other prescription medications and drugs of abuse throughout the study duration and for 1 week

prior to their participation in the study. They also had to refrain from alcohol and caffeine use 24 hours before testing, were not allowed to smoke during testing, and were not allowed to consume food 3 hours prior to arrival for testing. Treatments were single oral doses of alprazolam 1 mg IR, alprazolam 1 mg XR, and placebo. The study was a double-blind, placebo-controlled, three-way crossover design. Study medication was supplied at 9 a.m. on each test day, with a minimum period between testing days of 7 days. Before the first treatment, subjects received comprehensive training on the driving task. The standardized driving task was administered between 4 and 5 hours post-dose, at the time blood plasma concentrations of the XR formulation were expected to be at the maximum.

The driving test lasted one hour and was conducted in an instrumented vehicle over a 100 km (61 mi) highway while operating at a constant speed of 95 km/h (58 mph) and maintaining a steady lateral position between the lane lines of the right (slower) lane. Subjects were accompanied by a licensed driving instructor in a vehicle with dual controls. The standard deviation of lateral position (SDLP) was the primary outcome measure, and is a measure of road tracking error or "weaving."

Ten driving tests (7 under the influence of alprazolam IR and 3 under the influence of alprazolam XR) were terminated prematurely because the driving instructor judged the subject to be too drowsy to continue safely. SDLP scores were calculated from the data collected until termination of each ride. There was a significant treatment effect, with both drug formulations significantly increasing SDLP. The mean SDLP after alprazolam XR was significantly lower as compared to alprazolam IR. The IR formulation produced a mean increase in SDLP of 8.2 cm and the XR formulation produced a mean increase of 3.9 cm. However, the impairment was still severe with the XR formulation, equivalent to a blood alcohol level that is above .05 g/dL (the legal limit in many countries). It is concluded that the impairing effects of alprazolam XR 1 mg on driving performance were less than those of the IR equivalent dose, but still of sufficient magnitude to increase the risk of becoming involved in a crash.

The authors note that a study limitation is that the effects were assessed after a single dose. Alprazolam-induced impairment may become less severe after chronic administration, as tolerance to the sedating effects may develop after repeated use. However, they also note that tolerance to the impairing effects of benzodiazepines is never complete.

Skeletal Muscle Relaxants

Carisoprodol (Soma, Vanadom), an often abused drug, is a muscle-relaxing medication with CNS depressant side effects that is generally prescribed for managing acute lower back pain (Bramness, Skurtveit, Morland, & Engeland , 2007). The study objective of Bramness et al. was to determine if dispensing a prescription for carisoprodol was associated with an increase in motor vehicle crash risk by using population-based prescription, crash, and population registry databases in Norway. The pharmacy database (NorPD) covers the entire Norwegian population (4.6 million inhabitants). Exposure to carisoprodol was studied in community-dwelling patients age 18 to 69 who filled a prescription for carisoprodol, but did not fill a prescription for other impairing drugs during the study period. The other impairing drugs included natural opium alkaloids, benzodiazepine anxiolytics, and hypnotics. The Norwegian Road Accident Registry

(NRAR) provides information about motor vehicle crashes involving personal injury. Drivers age 18 to 69 involved in crashes during the study period were extracted for analysis. A third database (Norwegian Central Population Registry) was used to obtain demographic information on crash-involved patients. Data from the three databases were linked using the unique 11-digit identifier assigned to all individuals living in Norway.

Crash incidence among the exposed patients was compared to crash incidence among unexposed patients by calculation of a standardized incidence ratio (SIR). SIRs above one (1.0) indicate increased crash risk with personal injury as a driver. The SIR for a 7-day exposure period, across all age groups (n=66) was 3.7, and dropped to 2.4 for a 14-day exposure. The SIR for older males (age 55 to 69, n=2) was 1.5 and for older females (n = 6) was 4.1 after a 7-day exposure. The study authors indicate that their study findings are not surprising, based on the earlier studies that showed that carisoprodol may produce psychomotor impairment, that it may impair driving performance, and that it is issued to patients with a warning against driving motor vehicles. They note that physicians should be made aware of the potential driving problems connected with the use of carisoprodol, and should inform their patients of the risk.

Anti-Diabetic Medications

Hypoglycemia is a common side effect of some anti-diabetic medications that can result in cognitive-motor slowing and loss of consciousness. Hemmelgarn, Levesque, and Suissa (2006) conducted a case-control study using linked insurance databases in Quebec to assess whether the use of anti-diabetic drugs (specifically insulin, sulfonylureas, and biguanides) by older drivers increases their crash risk. The only biguanide in Canada at the time the study was conducted was metformin. Cases included 5,579 drivers age 67 to 84, who had been in an at-fault injurious motor vehicle crash, and controls included 13,300 older drivers who were not crash involved. Anti-diabetic drug exposure was assessed for the year preceding the date of the motor vehicle crash for cases and a randomly selected date during the follow up for the controls. Anti-diabetic drug exposure was also assessed during the 30 days prior to the index date to reflect current exposure. Exclusion criteria for cases and controls were: residence in a long-term care setting during the study period; hospitalization in the 60-days that preceded the index date; and hospital admission in the year before the index date lasting 30 days or more. Exposure was defined as the dispensing of at least one prescription for an anti-diabetic agent. A reference group of cases and controls was defined as those not using any anti-diabetic agents in the year preceding the index date.

A rate ratio of injurious motor vehicle crash for all anti-diabetic drugs was estimated using logistic regression. Rate ratios were adjusted for potentially confounding effects of age (within 1 year), sex, previous motor vehicle crash, and place of residence (rural or urban). The use of central nervous system (CNS) agents and the chronic disease score (excluding diabetes) were also evaluated as possible confounders using a change-in-estimate method. Rate ratios were adjusted for these factors only if the resulting estimate changed by more than 10%. Use of CNS agents was defined as receipt of a prescription for any of the following medications within 60 days preceding the index date: benzodiazepines and other sedatives/hypnotics; analgesics; antidepressants; tranquilizers/anti-psychotics; lithium; and centrally acting muscle relaxants. The chronic disease score was based on patterns of selected medication use in the preceding year, and

includes medications used to treat chronic conditions such as heart disease, hypertension, and respiratory disease.

The adjusted risk of injurious motor vehicle crashes for current users of any insulin was 1.3 relative to non-users, with the use of insulin alone higher at 1.4. The adjusted rate ratio for the combined use of insulin and oral agents was 1.0, indicating no increased crash risk.

Use of oral hypoglycemics only (no insulin) was associated with no increased risk, with an adjusted rate ratio of 1.0 for use of sulfonylureas only and metformin only. However, the combined use of sulfonylureas and metformin (without insulin) was associated with an adjusted rate ratio of 1.3. Among individuals using oral agents, the risk of an injurious crash was greatest for those managed with high doses of combined therapy using sulfonylurea and metformin, for an adjusted rate ratio of 1.4. The rate ratios for current exposure to anti-diabetic agents were slightly higher than the ratios for any use in the year preceding the index date.

In summary, among drivers ages 67 to 84, the use of insulin alone or a combination of sulfonylurea and metformin, especially at high doses, is associated with an increase in the rate of involvement in injurious motor vehicle crashes of 30 to 40%. The authors note that metformin alone does not usually cause hypoglycemia, however it does when combined with a sulfonylurea. The use of insulin is associated with hypoglycemia. Use of insulin as well as the combined use of metformin and sulfonylurea in high doses is also associated with retinopathy and neuropathy (complications of more advanced diabetes). The authors recommend that for individuals treated with insulin alone or high doses of combined oral therapy, efforts to reduce their risk of injury due to motor vehicle crashes may include assessment of vision and peripheral neuropathy, and measurement of blood glucose levels prior to driving.

ILLNESS VERSUS MEDICATIONS AND THE RISK OF FALLS

This section addresses a recurring theme in assessing the behavioral consequences of medication usage among (older) people, i.e., gauging the risk associated with prescription and OTC drugs versus the medical conditions treated by the medications. It is included because the same medications that mediate falls risk—specifically with respect to cardiovascular adverse drug reactions—may also mediate motor vehicle crash risk.

Lee, Kwok, Leung, and Woo (2006) found that chronic medical conditions were often more important than medications in causing falls in high-functioning community-dwelling older people. They reviewed demographic data, falls history in the previous 12 months, medical diagnoses, current medications, and self-rated health for 4,000 ambulatory community-dwelling men and women over age 65 in an urban community in Hong Kong. The purpose of the investigation was to determine whether medical illnesses or the medications used to treat them were the cause falls in the older population. This study is included in this research update, because vehicle crash involvement in the elderly has been significantly associated with a history of falling in the past two years (see Staplin, Lococo, Stewart, & Decina, 1999), and as falling and crashing are two adverse mobility outcomes, they may share the same underlying causes.

In this sample, 19.7% of subjects reported at least one fall, and 5.9% reported two or more falls. After adjusting for age and gender, medications associated with any falls included: aspirin, diabetic drugs, nitrates, NSAIDS, and paracetamol. Medications associated with recurrent falls included: calcium channel blockers, diabetic drugs, nitrates, NSAIDS, aspirin, and statins. Psychotropic drugs including benzodiazepines, antidepressants, and antipsychotics were not significantly associated with any falls or recurrent falls.

Multivariate models were applied to determine the association between each medication and falls history (any falls) with adjustment to significant non-drug factors. Being female, having heart disease, and having shorter stride length were highly associated with falling. Eye disease was moderately associated with falls in the nitrates model. Lower body musculoskeletal pain, previous stroke, and eye disease were slightly associated with falls in all medication models. *The only medication that was significantly associated with <u>any falls</u> was nitrate* (OR=1.489, p<.027). Multivariate models were also run for recurrent falls. Again, being female and having a shorter stride length were strongly associated with recurrent falls. Eye disease was moderately associated, and heart disease and lower musculoskeletal pain showed a slight association. *Among medications, only anti-diabetics showed a significant association with <u>recurrent falls</u>* (OR=2.9, p=.001). Because the study cohort contained a large proportion of diabetic patients not on drug treatment (25.7%), direct comparisons between diabetics with anti-diabetic medication and those without this medication could be made. The study indicated that anti-diabetic medications were related to recurrent falls, but being diabetic was not. Thus, more advanced diabetes or hypoglycemics side effects of drugs could be the cause of falls among older diabetics.

Van der Velde, van den Meiracker, Pols, Stricker, and van der Cammen (2007) conducted the first prospective cohort study of geriatric patients to investigate the effects of withdrawal of all fall-risk-increasing drugs (FRIDs) on tilt-table test abnormalities. The tilt-table test evaluates how blood pressure is regulated in response to simple stresses. At times, the nerves that control blood pressure may not operate properly and may cause a reaction that causes the blood pressure to drop.[3] This reaction may produce a fainting spell or symptoms such as severe lightheadedness. Tilt-table testing can determine the likelihood that a patient is susceptible to this type of reaction. In the tilt-table test, patients lie down on a table and their baseline blood pressure and EEG are taken for 10 minutes. Then, the table is tilted head-up to 30 degrees, and blood pressure and EEG are taken again for 5 minutes in this tilted position. The table is then tilted head-up to 60 degrees, and measurements are taken for 45 minutes in this position. The table is then lowered to the flat position and a dose of isuprel is given, simulating the amount of adrenaline the body would produce when walking up a staircase. The table is then tilted to the 60-degree position and blood pressure and EEG are again taken for 15 minutes. If this portion of the test can be completed, the table is returned to the flat position, the dose of isuprel is increased, and the table is again tilted to 60 degrees for a third and final time.

Certain drugs increase the risk of falls in older people. These include psychotropic drugs such as antipsychotics, antidepressants, and sedatives, as well as cardiovascular drugs such as diuretics, type Ia antiarrhythmics, and digoxin (Leipzig, Cumming, & Tinetti, 1999). Cardiovascular adverse drug reactions include syncope (fainting or a sudden loss of

[3] The tilt-table test procedure was obtained from information provided on Columbia University Medical Center's Web page at http://hora.cpmc.columbia.edu/dept/syncope/tiltfaq.html

consciousness) and falling, and are thought to result from carotid sinus hypersensitivity (CSH), vasovagal collapse (VVC), as well as orthostatic hypotension (OH). Explanations of these cardiovascular abnormalities follow. The carotid sinus is the point where the common carotid artery, located in the neck, divides into its two main branches. The carotid sinus can be oversensitive to manual stimulation, which is known as "carotid sinus hypersensitivity." Manual stimulation can cause large changes in heart rate and/or blood pressure. Symptoms can be produced by turning the head, wearing garments with tight-fitting collars, or manual stimulation of the neck as when shaving or taking a pulse in the neck. Orthostatic hypotension consists of symptoms of dizziness, faintness, or lightheadedness which appear only upon standing, and are caused by low blood pressure. Vasovagal collapse (also known as vasovagal syncope and neurocardiogenic syncope) is a fainting spell that often occurs when upright, although it can occur while sitting. Often, there are no precipitating circumstances, and it is most likely to occur in situations such as: during a large meal in a warm restaurant; when watching a production in a hot theater; when flying; or after prolonged standing.[4] The majority of the fall-risk-increasing drugs are known to induce OH, VVC, and/or CSH, which may be causal factors in drug-induced falls (and by extension, to drug-related crashes, as falls and crashes have been associated). The study was conducted to determine whether the removal of FRIDs resulted in a reduction of falls, and in improvement in tilt-table test outcome (indicating normalization of cardiovascular abnormalities resulting from the drugs).

Study participants were 211 new, consecutive outpatients at a geriatric outpatient clinic, 65 and older, with a mini-mental status exam score of 21 points or higher and able to walk 10 m without a walking aid. Falls history was considered positive if at least one fall occurred in the previous year; 135 subjects had a positive fall history. All subjects underwent tilt-table testing at baseline. First, carotid sinus massage was performed. CSH was defined as a fall in blood pressure greater than 50 mmHg or asystole (a state of no cardiac electrical activity) of 3 seconds or more. OH was measured for the first 5 minutes of head-up tilt after 10 minutes of quiet resting. OH was defined as a 20-mmHg fall in systolic blood pressure or a 10-mmHg fall in diastolic blood pressure. To provoke VVC, head-up tilt was continued until collapse occurred or 30 minutes of head-up tilt was reached. VVC was defined as a fall in blood pressure greater than 50 mmHg or asystole of 3 seconds or more.

Following tilt-table testing, all potential FRIDs were considered for withdrawal in the subgroup of fallers. FRIDs were able to be discontinued for 65 patients and dosages reduced for 6 patients. The subgroups of drugs withdrawn included psychotropics (sedatives, antidepressants, and neuroleptics), cardiovascular (antihypertensives, nitrates, antiarrhythmics, nicotinic acid, and timolol eye drops), and others (analgesics, antivertigo preparations, hypoglycemics, and urinary antispasmodics). Sedatives and antihypertensives were the largest two groups of drugs withdrawn. At a mean follow-up period of 6.7 months, tilt-table testing was repeated. Findings indicated that although overall FRID withdrawal was favorable for normalizing tilt-test-table results, it was significant only for OH. For the subgroup of patients who had cardiovascular FRIDs withdrawn, there was a significant reduction in OH and in CSH. This indicates that a substantial subgroup of geriatric patients experiences drug-induced cardiovascular adverse

[4] PatientPlus Web site at: http://www.patient.co.uk/showdoc/40001942/ and http://www.syncope.co.uk/neurocardiogenic_vasovagal_syncope_causes_of_fainting.htm

events, which are reversible after withdrawal of these drugs. For VCC, cardiovascular FRID withdrawal appeared favorable, but it was not statistically significant.

The association between cardiovascular improvements and nonoccurrence of falls during follow-up was also significant. Given the significant association between normalization of tilt-table test outcomes and nonoccurrence of falls, Van der Velde et al. (2007) comment that it is likely that part of the reduction in falls after FRID withdrawal in this cohort of geriatric patients was due to improvement in OH and in CSH. In this study, FRID-related falls were mediated through cardiovascular side effects.

Feasibility of Analyses Using Large Administrative Databases

Overview of Candidate Databases

This project task examined the feasibility of collecting and analyzing data from a National database and from at least two other large, administrative databases to improve our understanding of the associations between multiple medication use among older adults and motor vehicle crashes. These future analyses would support case-control studies by identifying the relative frequencies of various combinations of medications used by those with and without motor vehicle crash involvements in a given period of time.

The National databases chosen for review were the Medicaid Analytic eXtract (MAX) files; the Medicare Current Beneficiary Survey (MCBS) and associated Access to Care files, and the Cost and Use files; and the Veteran's Health Administration (VHA) Pharmacy Benefits Management (PBM) database. Requests for information about other national databases were also made to the Agency for Healthcare Research and Quality) regarding its research program called the Centers for Education and Research on Therapeutics and associated databases, and specifically to the HMO Research Network.

The General Practice Research Database in the United Kingdom was also reviewed in this task; with 3 million active patient records and 35 million patient-years of data, it is the world's largest source of primary care data from a single country. It also appears to be the most comprehensive database included in this review, in terms of the data elements it contains. However, the GPRD is very costly to access; and, it is unclear that analysis outcomes using this resource would generalize to U.S. experience, given the cultural and infrastructure differences between the two countries.

Additional, large administrative claims databases – including Kaiser Permanente and Independence Blue Cross – were identified as potential candidates but were judged less desirable according to criteria detailed in this report, and were excluded from further, in-depth review. However, a proprietary research database (Ingenix LabRx) using United Healthcare data, operating under the parent company UnitedHealth Group, was selected for detailed review.

Nine database administrators were contacted in this task. Based on responses from each to a questionnaire, and follow-up telephone calls, the leading candidates for future NHTSA data mining activities appear to be (1) the VHA/PBM database; and (2) the Ingenix LabRx database. The VHA/PBM, which appears to be a good choice overall, requires a caveat: a VHA collaborator on the research team is mandatory in the type of work envisioned by NHTSA. Because of the close scrutiny of all data entered in insurance claims among contributing organizations, the Ingenix LabRx database may offer the most accurate and reliable data among the present alternatives.

This chapter describes pertinent characteristics of each administrative claims database identified as a potential candidate for NHTSA research purposes and discusses its strengths and weaknesses, to provide a rationale for the included recommendations. An overview of the most salient features of each database reviewed herein is provided in Appendix H. Appendix I presents a set of questions sent to administrative claims database administrators to obtain the

information needed for the detailed review of their appropriateness for NHTSA investigations of medication usage and driving safety.

Detailed Review of Administrative Databases

A "straw man" in evaluating the strengths and weaknesses of each candidate database is to consider what an ideal database would be to support future NHTSA research on this topic. The ideal database would contain patient-level information on multiple millions of people[5] who have been continuously enrolled in the insurance program for at least 6 months and preferably for one year or more. This database would contain linked medical, hospital, and pharmaceutical data for each eligible person, and, ideally, would be the *only* provider of service for each eligible person. All prescriptions obtained would be through the insurance provider, so that a complete record of drug utilization would be captured in the claims database. Data fields would include:

- Dates of inpatient and outpatient hospital and doctor services;
- Diagnosis codes to document the reason for the healthcare visit, including E-codes with 4 digits to indicate external causes of injury for all injury diagnoses (so claims resulting from a motor vehicle cash may be identified, and the injured person may be identified as either the driver or a passenger);
- Patient demographics, including date of birth/age, gender, and ZIP code of residence;
- Pharmacy data including:
    - Drug dispensed (NDC);
    - Therapeutic drug class (decoded);
    - Active ingredient;
    - Quantity and date dispensed;
    - Drug strength;
    - Days supply;
    - Dollar amounts;
    - New fill/refill/partial indicator; and
    - Medical condition for which drug prescribed.

Not surprisingly, the present review, conducted in 2006, failed to identify such an ideal database. Details describing the following candidates for future analyses complete this chapter:

- Medicaid Analytic eXtract Database;
- Medicare Current Beneficiary Survey;
- VHA Pharmacy Benefits Management Database;
- General Practice Research Database (United Kingdom);
- Nationwide Inpatient Sample/Healthcare Cost and Utilization Project;
- Kaiser Permanente;
- Independence Blue Cross;
- Ingenix LabRx (United Healthcare) Database;
- The Centers for Education and Research on Therapeutics; and
- HMO Research Network.

[5] Based on the PharMetrics analysis reported by Leroy et al. (2004), it may be anticipated that 15-20% of all patients enrolled in the database will be 65+; but, only 5-8% of crash-involved patients will be in this older cohort.

Medicaid Analytic eXtract Database

Information describing MAX data was obtained from the following two Web sites: www.cms.hhs.gov/MedicaidDataSourcesGenInfo/07_MAXGeneralInformation.asp#TopOfPage and www.cms.hhs.gov/MSIS. A contact with the Centers for Medicare and Medicaid Services provided additional information about the feasibility of use of the MAX data by NHTSA.

The MAX data – formerly known as State Medicaid Research Files – are a set of person-level data files on Medicaid eligibility, service utilization, and payments. The MAX data are extracted from the Medicaid Statistical Information System. The MAX development process combines MSIS initial claims, interim claims, voids, and adjustments for a given service into this final action event. Unlike fiscal-based MSIS quarterly files, MAX files are annual calendar year files.

MAX data are derived from MSIS, and because it is necessary to allow for the delay between service delivery dates and claims adjudication dates, the availability of MAX data for a particular time period lags behind that of the MSIS data. Since the MAX data contain individually identifiable data, they are protected under the Privacy Act. They are available for approved research activities only through a Data Use Agreement (DUA) with the Centers for Medicare & Medicaid Services. Note that only approved academic research projects and certain government agencies are entitled to a DUA to obtain MAX data.

Prior to Federal fiscal year 1999, the Medical Statistical Information System (MSIS) was a voluntary program and those States participating in the MSIS project provided data tapes from their claims processing systems to the Centers for Medicare & Medicaid Services in lieu of the hard-copy statistical 2082 tables. Beginning in 1999, the program became mandatory for all States.

MAX 2002, 2001, 2000, and 1999 data are available for all States and the District of Columbia. Data for all States and DC for 2003 became available in late 2006, and data for all States and DC for 2004 should be available in 2007.

There are 5 MAX data sets: (1) a Person Summary file; (2) an Inpatient Hospital file; (3) a Long-Term Care file; (4) a Prescription Drug file; and (5) an Other Services file. The Person Summary File contains one record for each person enrolled in Medicaid for at least one day during the reporting year. The file includes the enrollee's demographic data as well as annual and monthly Medicaid enrollment data. It also contains information regarding the person's eligibility for Medicare (known as crossover claims or dual eligibility). Finally, it includes an annual summary of Medicaid utilization and expenditures for each enrollee by major Medicaid types of service. The four paid claims files contain information from adjudicated medical service related claims and capitation payments. Four types of claims files representing inpatient, long term care, prescription drugs and non-institutional services are submitted by the States. These are claims that have completed the State's payment processing cycle for which the State has determined it has a liability to reimburse the provider from Title XIX funds. Claims records contain information on the types of services provided, providers of services, service dates, reimbursement amounts, types of reimbursement, and selected demographic variables. The Other Services file contains information on outpatient services, excluding pharmacy services (pharmacy charges are included in the pharmacy database).

Data validation reports provide a wide array of basic statistics on data elements from each State and file type. Data anomaly reports are available that document data inconsistencies (which can't be fixed) and work-around solutions. They also describe situations where data are valid, but unexpected results occur because of broken time series, newly covered services, etc.

Medicaid data limitations include those related to eligibility, services, payments, completeness, timeliness, and the lack of provider characteristics. In terms of eligibility, there is minimal information on other insurance coverage, there is no beneficiary name or address, income data are unavailable, and eligibility is not continuous for all enrollees—therefore there is eligibility "churning." The concept of churning eligibility means that eligibility for Medicaid is determined monthly, based on a categorical relationship to Medicaid entitlement (e.g., age, disabled, poverty adult or child, etc.), income and assets. Because circumstances change from month to month people may be enrolled in Medicaid intermittently—on and off the program. The services limitations include the following: services are included only during times of eligibility, only Medicaid-covered services are present (and coverage varies by State), services are incomplete for duals (only the residual after Medicare payment), and services are incomplete for people in prepaid plans. Payment limitations include: missing payments (due to aggregate adjustments, end-of-year settlements, and disproportionate share hospital), incomplete for third-party payments, and drug payment amounts are prior to rebates.

The database contact for the current project task provided some specific information about the feasibility of the MAX databases for future NHTSA analyses of medications and motor vehicle crashes. First, it was stated that the databases include data that are necessary to meet reporting requirements or to get medical claims paid. Therefore, some of the data that would be necessary for future NHTSA work may not be present. For example, although the agency manuals state that cause of injury codes and diagnoses should be coded, diagnoses and injury codes are often not required for payment, and researchers have found that cause of injury (E-codes) are dramatically underreported in Medicare and Medicaid data.

In a study population utilizing 5% of the Medicare-aged sample from 1997 to 1999, approximately 75% of the Medicare claims reporting an injury diagnosis (800-995) were <u>not</u> E-coded (Bishop et al., 2002). E-coding in the MAX database varies by State, by injury severity, and by site of fracture. Western and northern regions of the country report more E-codes than Midwestern and southern regions. The more severe the injury, the more likely that E-coding will be present. Strains and sprains are less likely to be E-coded than fractures. As an example, back sprains were associated with E-coding in 12% of the cases, compared to fractures of the femoral neck, which were associated with E-coding in 45% of the cases. Bishop et al. (2002) conducted a logistic regression on a 5% sample of aged fee-for-service Medicare beneficiaries in the year 1999. For the 48,636 fracture episodes, E-codes were present in 40% of the cases. Bishop et al. (2002) reported that E-codes are more frequently reported in fracture episodes for older elders; the odds ratio for an E-code for people age 75 to 84 was 1.06, compared to 1.13 for people 85 and older. In addition, the probability that a fracture episode for a rural beneficiary includes an E-code is 10% greater than that for an urban beneficiary. Fractures treated outside of a hospital are less likely to have an E-code (16% of the claims were E-coded), compared to fractures treated during an inpatient stay in the first week of an episode (57% of the claims were E-coded) and fractures treated in an emergency room without a hospital stay (54% of the claims were E-coded). Although the odds of E-codes in episodes with hospital care are low in States that require

cause of injury in hospital discharge data, odds are even lower in States with no E-code requirement for hospital discharge.

A further concern with the use of CMS Medicaid data is how E-codes are reported. In a memo commenting on motorcycle accidental E-codes in the Medicaid eXtract Analytic files for the year 2000, it was reported that when E-codes were reported, they were often reported using only the 3-digit code (Benedict & Brinker, 2005). To identify vehicle type, a 4-digit E-code must be reported. This would be problematic in future NHTSA research, because not only is vehicle type important (trains vs. automobiles versus trucks vs. motorcycles), occupant type (driver versus passenger) is important. The 4th digit must be present in an E-code to identify the injured person. Only drivers would be of interest in studies of vehicle crashes and medication use.

Another caveat to the use of the data is that prior to January 2006, coverage for prescription drugs under Medicare was nonexistent (except for limited coverage of drugs related to End-Stage Renal Disease and transplantation), so there is no pharmacy data for Medicare-only patients up to this date. Prescription drug data are available for Medicaid recipients (including dual Medicaid-Medicare enrollees), however. In 2002, the Medicaid database contained data for approximately 7 million individuals 65 and older. Prescription drug information is not available for inpatient hospital stays; because inpatient hospital bills aggregate the drugs into one cost center (no names are available). The outpatient medications are listed individually by NDC code, but the NDC code does not provide the therapeutic drug class. If that was required, a separate filter would need to be applied. Existing license agreements prevent CMS from sharing data that includes therapeutic use codes with third parties. Alternatively, the Food and Drug Administration maintains a free filter for therapeutic drug classification.

The lag between claims incurred for pharmacy claims and entry into the database should theoretically take no more than 45 days. But States vary in their compliance to these regulations, and there is no penalty for failure to comply with reporting requirements.

In order to gain access to the database, first the files required for research must be identified among the five available: Inpatient hospitalizations; Long term care; Prescription drug; other ambulatory services; and the Person file (includes Medicaid eligibility information). Then, the States of interest and years of interest would need to be identified. Access is governed by the Privacy Act/HIPAA. Requests for these files must include a study protocol along with a Data Use Agreement. The use of the files must then meet approval by the Privacy Board. CMS does no custom programming or data extraction. A CMS processing fee may apply.

Based on the "churning eligibility," the fact that E-codes are generally reported only for the most serious injuries (and many of those including only 3 digits), and the incomplete data resulting from dual eligibility, it doesn't appear that the MAX databases are the most robust among those evaluated in this task for the type of data-mining efforts of interest to NHTSA. CMS initiatives begun in 1998 may improve Medicare E-coding. A suggestion provided by an analyst at CMS[6] was to consider the possibility of linking the Medicaid research files to a State motor vehicle crash file and to an auto insurance crash file, with the most promising common variables being a Social Security number in each database and at least one other demographic, such as year of birth. The Medicaid research files contain an SSN and an individually assigned

[6] Beth Benedict, CMS/ORDI.

Medicaid identifier for each enrollee, but they do not contain driver license numbers or addresses. It would be important to obtain the State of residence of the individual being linked, and not the State where the crash occurred and is being reported from. It would be important to match the individual with the Medicaid research file from the State of residence. A fair number of motor vehicle crashes occur when people are driving out-of-State. An auto insurance database might provide a third linkage, providing a driver's license number and an address, and personal demographics.

Medicare Current Beneficiary Survey (MCBS)

Much of the information presented about the Medicare Current Beneficiary Survey CMS database was obtained from the CMS Web site[7], which presents detail on the interview population, as well as the two major files produced by MCBS: the Cost and Use File and the Access to Care File. A request for information was also sent to the director of the Enterprise Databases Group (Office of Information and Systems) at the Centers for Medicare and Medicaid Services, and to the Research Data Assistance Center at the University of Minnesota.

MCBS interview data are linked to Medicare claims and other administrative data to enhance their analytic power. The survey and claims data together constitute a more complete utilization data set for the MCBS sample than is available from either source. The final file consists of survey, administrative, and claims data. All personal identifying information is removed.

The MCBS is a continuous, multipurpose survey of a representative national sample of the Medicare population, conducted by the Office of Strategic Planning of the Centers for Medicare & Medicaid Services. The central goals of MCBS are to determine expenditures and sources of payment for all services used by Medicare beneficiaries, including co-payments, deductibles, and non-covered services; to ascertain all types of health insurance coverage and relate coverage to sources of payment; and to trace processes over time, such as changes in health status, spending down to Medicaid eligibility, and the impacts of program changes.

MCBS contains a variety of data on each sampled person, including topical supplements; combining survey and administrative data. Beneficiaries sampled from Medicare enrollment files (or appropriate proxies) are interviewed in person three times a year using computer-assisted personal interviewing (CAPI). The first round of interviewing was conducted from September through December 1991, and the survey has been continuously in the field since then. The data are designed to support both cross-sectional and longitudinal analyses. Interviews at 4-month intervals are designed to yield longitudinal series of data on the use of health services, medical care expenditures, health insurance coverage, sources of payment (public and private, including out-of-pocket payments), health status and functioning, and a variety of demographic and behavioral information, such as income, assets, living arrangements, family supports, and access to medical care.

The MCBS contact for this database review task advised that the MCBS would not be a feasible data set for future NHTSA research on older drivers, medications, and crashes, because it does not contain any prescribing information, other than self-reported prescription drugs. There

[7] http://www.cms.hhs.gov/apps/mcbs/default.asp

are no pharmacy or prescription claims data; only self-reported medication use. So there is no way to determine if a survey respondent was taking a prescription drug on the date of service for a Medicare claim. In addition, the Medicare claims data include E-code data, but it is unreliable (i.e., it is only available when an E-code is required for billing purposes). None of the MCBS survey questions relate to motor vehicle crashes. Finally, information in the database relating to Medicare HMO utilization and other insurers and payers outside of Medicare is based on self-reported information and imputation.

Veteran's Health Administration Pharmacy Benefits Management Database

Three research studies using the VHA PBM database deserve mention in this chapter, as certain variables, procedures, anomalies, and limitations revealed therein speak to the feasibility of using the database to associate medication use and motor vehicle crashes (a specific type of adverse event).

In the first study, French, Campbell, Spehar, and Angaran (2005) linked outpatient prescription data with clinical data to develop a risk adjusted binary model that associates benzodiazepine use with the risk for a healthcare encounter for an injury. They used 3 years of outpatient benzodiazepine prescription data (totaling 133,872 outpatient prescriptions) for 13,745 patients for a VA medical center (James A. Haley VA Hospital in Tampa, FL). The PMB database contains information on the strength of the drug, prescribed daily amount, fill date, quantity supplied, and a unique patient identifier. The daily milligrams consumed was computed as the product of the prescribed daily amount (number of pills) and strength (mg) and then converted from daily milligrams consumed to daily oral dosing equivalents or valium equivalents. Using the patient identifier, the pharmacy data were combined with VHA healthcare utilization data extracted from the centralized VHA National Patient Care Database. This database includes patient demographics, injuries, and diagnoses. Dates of the injuries were unavailable in the database; the researchers used the date of the associated healthcare encounter (inpatient admission and outpatient clinic visit). Primary and secondary diagnoses using the ICD-9-CM codes 800-999 for injuries and poisonings in both inpatient and outpatient datasets were examined. Only those encounters associated with an injury code while receiving benzodiazepines were used in the analyses and only the first injury episode of care while using benzodiazepines was used, to avoid analytical problems with multiple episodes for one patient. Certain injuries were excluded, as they were unlikely to result from benzodiazepine use. These included complications devices, implants, grafts, and complications of surgical procedures or medical care. These were identified using the Agency for Healthcare Research and Quality Clinical Classification Software (CCS) that aggregates the injury ICD-9-CM codes into homogenous diagnosis groups. Thus, CCS categories 237 and 238 for the two types of complications were removed. Also, because of coding anomalies, CCS category 227 (spinal cord injuries) were removed. Anomalies resulted with this code because almost all spinal cord injury patients were being treated for follow-up care, as opposed to being treated for the original spinal cord injury.

Controlling for co-morbidities (secondary diagnoses that did not relate to the principal diagnosis, screened through a diagnosis related group) and demographic factors (age and marital status), French et al. (2005) found that increases in dose and duration were associated with an increased risk for an injury-related episode of care. Increasing the dose by 1 U (valium equivalent) may increase the risk of injury on average by 6% and a 1-U increase in duration (one additional week on the drug) may increase the risk by 4%. The authors note a limitation to the

study is that the sample was overwhelmingly male, and thus generalizability of the results to females is questionable. Also, the mechanisms of injury (E-codes) could not be ascertained for all injuries under study because of the lack of E-coding for most of the healthcare injury encounters. Preliminary analyses found that less than 50% of injury discharges in the VHA system have an E-code. However, this compares to national studies of civilian injury hospitalizations where E-coding was present for 60% of the discharges (Shinoda-Tagawa & Clark, 2003).

In the second study, French, Chirikos, et al. (2005) evaluated the concomitant use of benzodiazepines and other drugs on the likelihood of an injury-related healthcare episode. They used the VHA data from the pharmacy benefit management system for the James A. Haley VA Hospital, as described earlier. Drug combinations were limited to those defined by Micromedex software likely to result in major interactions. Pair-wise combinations of a benzodiazepine and one of the other medications were then constrained to just those being used within the 30-day period prior to the date of the healthcare encounter for the injury. There were a total of 54,591 prescriptions involving the concomitant use of benzodiazepines and other drugs for 6,223 unique patients. Results indicated that 12.7% of the patients with concomitant use of benzodiazepines and other drugs had an injury or adverse event, as compared with 4.3% of the patients taking benzodiazepines who did not have concomitant drug use. The most common combinations were benzodiazepines with a muscle relaxant (17% of the concomitant prescriptions) and opioids (79% of the concomitant prescriptions).

More recently, French, Campbell, et al. (2006) used data from the national VHA ambulatory event database to identify which specific medications (within recognized major problematic drug categories that increase risk of falling) were prescribed to veterans before their outpatient treatment for a fall. The database includes data from all 21 Veterans Integrated Service Networks for approximately 5.1 million unique patients with approximately 72 million outpatient encounters. The study population was all VHA patients age 65+ who had a fall-related outpatient encounter (as indicated by a diagnostic E-code) during the year 2004 and who received one or more outpatient medications during the study period. Using unique encrypted patient identifiers, the encounter data were merged with outpatient pharmacy data from the VHA decision support system (DSS) for the same year. The DSS pharmacy data contains information on the drug, fill date, and quantity supplied for each patient. It does not include medications filled outside of the VHA system, or information on nonprescription drugs, or drug samples acquired independently by the patient. The authors note, however, that many veterans have an incentive to use the VHA for their medications because of the low VHA co-payment. The researchers identified patients with a fall-coded encounter and exact age and sex matched comparison subjects from a pool of over 180,000 outpatient nonspecific chest pain patients, because nonspecific chest pain is one of the most common reasons for outpatient visits and an important symptom in cardiovascular disease, and to analyze differences in particular medications between this patient group and the group that fell. Fall related injuries due to slips, trips, or falls unrelated to transportation were identified by E-codes E860-E888). Records were included in the analysis if a fall E-code appeared in any of the 10 diagnosis fields (1 primary diagnosis and 9 secondary diagnosis fields).

The drugs of interest were in three major drug categories: central nervous system (CNS), cardiovascular system (CVS), and musculoskeletal system (MSS). The most comprehensive and evidence-based published list of specific problematic fall-related medications is the Canadian

Safety Council's Risk Assessment tool, which is divided into classes with generic and trade names. The data from the DSS outpatient prescription file only contain information about drugs on the VHA formulary, therefore, drugs from the Canadian fall risk assessment tool and the Beers Criteria list were reclassified using the U.S. national drug code. Linking of outpatient medications and outpatient encounters was temporarily constrained, and included only those medications actively prescribed up to the time of the encounter. There were 20,551 patients with fall-coded encounters and 20,551 exact age- and sex-matched comparisons. Of the patients selected for the study, 95% were male. There was no significant difference in the number of patients who used fall-related medications in the nonspecific chest pain group and fall-coded group. More patients with nonspecific chest pain received CVS medications and more patients with fall-coded encounters received CNS medications. There were no statistically significant differences in the overall MSS category between the two groups, but more patients in the nonspecific chest pain group than in the fall-coded group used (prescription) non-steroidal anti-inflammary drugs. Within the CNS category, significantly more fall-coded patients used opioid analgesics and narcotics, hypnotics, anti-Parkinson agents, and the psychotropic drug classes of cholinesterase inhibitors, anticonvulsants and barbiturates, antidepressants (including SSRIs, tricyclic antidepressants, and others), antipsychotics (including both atypical antipsychotics and typical neuroleptics) and benzodiazepines. There were no differences between groups in the use of antihistamines and antinauseants.

One limitation to French, Campbell, et al. (2006) study (other than the population being limited to veterans and mostly males) is that some veterans can receive care under the Medicare program from non-VHA providers and facilities, and that these data were not captured in the analyses. The authors state that future research at the Patient Safety Center in Tampa, Florida, will link available Medicare data from the U.S. Department of Veterans Affairs Medicare data sets so that this health care utilization is captured.

French, Campbell, et al. (2006) note that this is the first national study of veterans that examined their outpatient use of particular drugs temporally linked with a fall-coded health encounter. This study is of particular interest to the current topic of examining multiple drug use and vehicle crashes. In the past NHTSA study of polypharmacy, classes of drugs were identified as being potentially driver impairing and were linked to increased crash risk in older drivers using a non-proprietary database. The list of drug classes and specific medications developed in that project (available at www.drivinghealth.com/PDIdrugindex.html) could be used by NHTSA in future research with the VHA PBM database. French, Campbell, et al. (2006) state that no U.S. medication safety studies have been based on National outpatient medication data linking information about outpatient prescriptions, including dosing and timing, to health care utilization associated with injuries. They state that, *"The data available through the VHA system allows one to study the association between a particular drug and an injury or adverse event by identifying a population at risk and then linking outpatient medications with healthcare utilization in that population."* They further state that in their opinion, there is no other comparable National drug safety research capability that includes a National electronic medical record and data on health care utilization across as many care settings in the United States.

French, Campbell, et al. (2006) indicated that comprehensive National outpatient medication usage data at the patient level are currently not available for researchers from the Medicare program. The new Medicare Part D outpatient medication benefit was implemented in January 2006. Because of the large number of private Medicare prescription drug plans with

nonstandard formularies, they state that it is not clear how, when, or if any of the outpatient medication data in the Part D benefit will be available to researchers. They further state that countries with national health care systems (Canada, Australia, Finland, Sweden, and the United Kingdom) and large managed health care systems in the United State currently have the ability to link data in such a way.

Contact with the program manager of Outcomes Research at the VA Center for Medication Safety revealed that there are 8 million veterans nationwide who use the VA for health care. Of this group, over 5.1 million get their prescriptions from inside of the VA system. Some of these patients who are 65 and older may use outside systems to obtain their medications, but it is rare, based on the fact that the co-pay for VA medications is so low (only $8 per prescription). There are cases where a VA patient may go to a non-VA facility for health care, as in the case of an acute condition, where an ambulance takes the patient to the closest hospital that may be non-VA. It is sometimes possible to link with the Medicare database, but the Medicare database is two years behind in claims, whereas the VA system is current to within three months. But, the patients always return to VA centers for follow-up, so their information will be picked up at their next regular visit. Although the VA population includes physically and cognitively disabled people who would not be drivers, a "fair number" of the veterans are drivers. Motor vehicle crashes are coded in the VA database. While drivers and passengers are not separately identified, the database contains ICD-9-CM E-codes, so presumably the 4th digit identifying the injured person as a passenger or driver is present. The VA PMB database includes data for both inpatient and outpatient health care visits. It is a nomenclature-based database, so exact drug names, rather than drug codes are included. The exact drug names can be easily matched to the NDC codes, however.

A potential drawback to the use of this database is that it has been historically proprietary, and can only be used by non-VA researchers if a collaborative agreement is made with an investigator within the VA. Alternatively, the data has been made available if a VA employee is on staff with the researchers. The VA doesn't provide a data file to anyone other than a VA collaborator. This is due to HIPAA requirements, as well as the need for internal knowledge of the VA database and its coding to ensure the accuracy of the results." In order for the VA to release data, NHTSA and its researchers would need to identify the kind of information needed and provide an analysis plan, and then the VA IRB would review the request. They would only provide the data to the VA principal investigator or a research member who is affiliated with the VA. Costs for data range from $8,000 to $150,000. The cost for data and data cleaning for a study population of 40,000 (the magnitude of the French, Campbell et al., 2006 study) would run approximately $30,000. This covers the costs of pulling ICD-9 codes and medicines. If data analysis were required by VA staff, the salary of programmers and statisticians would need to be covered. This would increase the cost by an additional $25,000 to $75,000. Requests would need IRB approval from both the researchers and the VA IRB. In summary, it appears that this database contains all the necessary elements to perform analyses of interest to NHTSA. The only drawback is the inability to obtain an extracted dataset for independent work, if a non-VA researcher is proposed.

General Practice Research Database

The General Practice Research Database is operated by the GPRD Division of the Medicines & Healthcare products Regulatory Agency in London. The GPRD is considered by

many as the "gold standard" of longitudinal anonymised patient databases from primary care, and its usage has resulted in over 400 clinical reviews and papers.[8] With over 3 million current patient records (8.9 million total) and over 35 million patient years of data from over 350 practices, it is the world's largest source of longitudinal primary care data covering the full cross-section of the population in the UK. GPRD contains comprehensive data from real life clinical practice on diagnoses, prescribing, ADRs, co-prescription, co-morbidity, dosage details, off-label prescription, and patient age, sex and other demographic details. The data are anonymised and collected directly from records held on general practitioners' surgery computers.

Information obtained from the GPRD Web site is presented below, supplemented by comments from the head of GPRD/GPRD Group.

There are several ways to access Full Feature GPRD (FF-GPRD), either as datasets, through commissioned research and reports or through secure on-line access. Unlike flat files, the database is pre-structured and ready to query online, minimizing the need for IT support. This is cost-effective because it saves time and resources compared to building and periodically updating datasets. Included as part of the online access licenses are software packages and tools for constructing queries, and results can be exported for further analysis to most statistical spreadsheet packages. The GPRD Division has an experienced research team who assists customers with queries, advises on study design and carries out additional commissioned research projects. Best practice guidance is issued as new methodologies are developed, allowing customers to make the most of the system and the data. These services complement the comprehensive training included with all online access packages. Additionally, online access customers are supported by the Helpdesk to help resolve any IT-related issues.

As some GPRD customers may not have the resources to have continued access to FF-GPRD via the on-line services, datasets for single study analysis may be provided. Datasets are built from the FF-GPRD but are static representation of the data. Datasets are usually supplied, following ISAC approval on a CD-ROM. Charges are based on the number of patients and the data element required.

A direct contact with GPRD provided additional information about the feasibility of using this database for future studies of medications and crashes. While the clinical data (medical, basic hospital care, and pharmaceutical care) are within one database called the GPRD, what NHTSA studies would require is external linkage via the National Health Service 10-digit ID to National Hospital Episodes data for patents who are hospitalized and to other more regional datasets for patients who attend the emergency room but are discharged without being admitted to a hospital bed. The GPRD is a generalizable, "5.5% of the UK population based dataset." Patients 65 and older make up approximately 17% of the sample.

In the United Kingdom, the general practitioner is the gatekeeper to all care, and as such, stores not only primary care information, but essentially all details of care. Linkage of medical, hospital, and pharmaceutical data is via a unique patient identifier (the NHS 10-digit unique ID). Diagnoses are coded using the ICD10 (ICD9 for earlier data) and READ. Four-digit coding is used with up to 12 ICD codes allowed after the primary code. Codes V40.n to V48.n are available to distinguish car related events and the driver (.0, .5, or .9) and equivalent codes for

[8] See http://www.gprd.com/whygprd

lorries, buses, etc. Codes identify when a patient is a passenger or the driver. Procedures are coded using the OPCS4; and pharmaceutical claims are coded using the British National Formulary, ATC code, and UK-wide Multilex. ICD9 E-codes (coded by coding clerks) are present in the database. The percentage of injury discharges with an E-code could be made available to us at a later date, if required. Dates of motor vehicle crashes are unknown; the data of first admission for care relating to a crash would be used as the data of the crash, for analyses. The database includes socioeconomic class and regional markers (rather than zip codes). Privacy rules would allow the release of patient age; date of birth would be released by year only. Also, patient gender is available for release.

The database contains information that would allow the identification of what prescriptions were filled or refilled within a specified window of time, in proximity to a motor vehicle crash. Prescriptions are based on a 28-day cycle. There may be some level of misclassification, because some prescriptions might not be picked up; but, the sequence of prescribing for chronic drugs will indicate, for the most patients, this will not be an issue. Dates are associated to the date that the prescription was written, not filled. For acute drugs, this is known to be an accurate marker, and for chronic drugs, the sequence of refills is the key. All drug coding is done to the names of individual drugs (using generic names). The following information about drugs is also available: medical condition for which the drug was prescribed (from the linked consultation ID file of therapy and diagnosis); drug name, active ingredient, and NDC code; quantity provided; strength; decoded therapeutic class; and day's supply.

The database contains all information for a patient, regardless of what physician and what pharmacy was used (the database is NHS total care). Variables are not available (nor are they necessary) to indicate whether a patient has other coverage; there is a small volume of private care in the United Kingdom, but this would not significantly bias the research that could be undertaken. Because of the NHS and the fact that there is no charge for those over age 65 and those with chronic conditions, together with the relatively low charge for others, 99% of the drugs used are obtained through the NHS system. Only over-the-counter (essentially, the very safe drugs) are obtained outside of the NHS.

Data are available to the GPRD approximately one year after a claim is made (i.e., the lag time is one year). Continuity of eligibility is tracked via the patient roster file, as NHS care is cradle to grave for essentially 99.9% of the U.K. population.

The cost of having selected fields extracted from the database and anonymized could not be provided by the database contact, without further detail about the studies (e.g., the protocol). The GPRD Web site provides the following range of costs for the listed services.[9]

- Online access £30,000 to £325,000 per year.
- Datasets £8,000 to £65,000.
- Commissioned studies £30,000 to £250,000.

The procedure to obtain the data would be to submit a protocol, and then have it undergo approval by the relevant Scientific and Ethical committees. The GPRD team would advise on the

[9] In June 2006, 1 British pound = 1.8517 dollars

procedures necessary. A linking agreement would also be required from a committee called PIAG. There would be no barriers to the release of the data to NHTSA; however, it would need to be under legal agreement and the study must be published.

The completeness of the GPRD recommends it for future NHTSA data-mining activities. However, it may be cost-prohibitive. Also problematic are the substantial differences in the availability of/access to public transportation facilities; geometric and operational characteristics of streets and highways; licensing policies/practices; and gasoline costs (and therefore miles driven per capita) that differ between the two countries, and that may call into question the generalizability of U.K. analysis outcomes to the United States.

Nationwide Inpatient Sample/Healthcare Cost and Utilization Project

Information about the NIS was obtained from the NIS Web site,[10] i.e., there was no direct contact with a database administrator, other than an e-mail inquiry to User Support. According to the NIS Web site, NIS is the largest all-payer inpatient care database in the United States. It contains data from approximately 8 million hospital stays each year. NIS 2003 contains all discharge data from 994 hospitals located in 37 States, approximating a 20% stratified sample of U.S. community hospitals. The sampling frame for the NIS 2003 is a sample of hospitals that comprises approximately 90% of all hospital discharges in the United States.

NIS is the only national hospital database with charge information on all patients, regardless of payer, including people covered by Medicare, Medicaid, private insurance, and the uninsured. NIS's large sample size enables analyses of rare conditions, such as congenital anomalies; uncommon treatments, such as organ transplantation; and special patient populations, such as children. NIS data are available from 1988 to 2003, allowing analysis of trends over time. The number of States in the NIS has grown from 8 in the first year to 37 currently.

For most States, NIS includes hospital identifiers that permit linkages to the American Hospital Association's database and county identifiers that permit linkages to the Area Resource File. The NIS contains clinical and resource use information included in a typical discharge abstract, with safeguards to protect the privacy of individual patients, physicians, and hospitals (as required by data sources). The NIS can be weighted to produce national estimates. The NIS excludes data elements that could directly or indirectly identify individuals. Purchase of the files is open to all users who sign a Data Use Agreement (PDF file, 55 KB; HTML). Users must agree to use the database for research and statistical purposes only and to make no attempts to identify individuals.

Identities of institutions are available only in States where data sources already make that information public or agree to its release. For these institutions and for research purposes only, linkage is possible to data from the Annual Survey of the American Hospital Association.

An e-mail contact was made to HCUP User Support to determine whether medication use and injury codes were included in the datasets. HCUP User Support replied that HCUP data include ICD-9-CM external cause of injury codes (E-codes) and previous studies have found the E-code data fairly complete and reliable (Barrett, Steiner, & Coben, 2004). Barrett et al. (2004)

[10] http://www.hcup-us.ahrq.gov/nisoverview.jsp

found that across 33 States that provided inpatient data to HCUP, E-code completeness on injury records averaged 87.2%. For inpatient data, motor vehicle traffic accounted for 18.2% of all unintentional injuries. Across the nine States that provided emergent department data to HCUP, E-code completeness on injury records averaged 92.5%. In these nine States, motor vehicle traffic accounted for an average of 12.1% of the unintentional injuries.

Although E-code data are complete and reliable, HCUP does not include complete or reliable pharmacy data, nor can HCUP data be linked to pharmaceutical data. Thus, it would not be possible to determine what prescriptions were filled or refilled within a specified window of time. Since it would not be possible to identify medication use for patients hospitalized with injuries resulting from motor vehicle crashes, the NIS database would not be feasible for future NHTSA data-mining activities.

Kaiser Permanente

The database contact stated that Kaiser does not sell or distribute data; it would not download data and provide it to NHTSA or its researchers. Further, it only does research in-house, and only when it is of value to its members. In order to engage in research on medications and crashes among the older population of members, Kaiser would first need to find a collaborative researcher in-house with an interest in the topic. It would then require the use of its own investigator, statisticians, and programmers to complete the work, according to a research plan that NHTSA would provide, under a formal contract to ensure that its research costs were covered.

Kaiser Permanente has 8.3 million members distributed throughout 8 regions nationally, the largest of which is the Northern California region with 3.3 million members. In the Northern California region there are 600,000 members age 65+. There are presently 80 databases that can all be linked through each member's 7-digit membership number. Many months into the future, a new database—HealthConnect—will be installed, which contains most of the fields presently existing in the 80 databases; the new database will then need to be verified before it can be used. The present databases contain inpatient, outpatient, and emergency room medical data. The kinds of data that are included in the databases are diagnoses, radiology, pharmacy data, clinical laboratory data, and pathology. It is unknown whether etiology data (the reason for the visit) are present in any of the databases. The database contact did not know whether motor vehicle crashes were coded, although they could be obtained through chart review, and future encoding. If E-codes are not presently included in the databases, the cost for chart review would likely be prohibitive.

Based on the fact that Kaiser cannot provide a data set to NHTSA or its researchers, and the high likelihood that E-codes for motor vehicle crashes are not presently part of the databases, the use of the Kaiser databases for future NHTSA research is not recommended.

Independence Blue Cross

A contact at Independence Blue Cross provided several reasons that the Independence Blue Cross (IBX) database would not be feasible for use in future NHTSA research. First, IBX outsources all drug claims for payment; this means that there is no mechanism to link pharmacy data with claims data relating to injuries. Second, it's questionable whether coding for injuries

goes beyond coding for diagnoses. It is very likely that there are no E-codes present in the database. Finally, the IBX legal department expressed concern regarding patient privacy, and advised that a separate authorization would need to be sent to all patients to obtain their permission (to comply with HIPAA), even though our description of the future work specified that any files obtained would be anonymized.

Ingenix LabRx Database (United Healthcare data)

Ingenix LabRx is a proprietary research database that incorporates de-identified medical and pharmacy claims, lab results, and enrollment data on more than 35 million lives spanning 4.5 years (a National managed care population). Of particular interest is that the database has more than 21 million continuously enrolled covered lives for 12 months. A database contact indicated that it would be feasible to use the LabRx database in future NHTSA data mining research, as this type of work is performed quite frequently using LabRx.

LabRx is a database linking five datasets: administrative data, pharmacy claims data, physician and facility claims data, lab test results data, and consumer elements. It contains 35 million people with both medical and pharmacy benefits between May 2000 and December 2005. There are 55 million lives covered in the United Health Care Group, interacting with 450,000 physicians and 5,000 health care institutions. Of the 35 million lives included in LabRx, 61% have at least one pharmacy claim. Only 5.5% of this population (1,943,152) is 65 or older. However, although the number of lives covered drops significantly as age approaches 65, this will change dramatically in the coming years, because United recently acquired Pacific Care (a Medicare and Supplemental carrier) and Ovations (the largest Medicare provider in the Nation).

Within the population of 35 million lives, approximately 33 million are covered by commercial insurance, 1 million by Medicaid, 700,000 by Medicare, and 4,000 by other or unknown payers. It contains approximately 14 million covered lives per year, and is updated monthly. The data are blinded to protect patient privacy, yet the database supports patient-linked longitudinal analyses.

The data elements included within each of the five data sets are listed below.

Administrative Data: Member Identifier; Plan; Gender; Age; Dates of Eligibility.

Pharmacy Claims Data: Member Identifier; Prescribing Physician; Drug Dispensed (NDC); Therapeutic Drug Class; Quantity and Date Dispensed; Drug Strength; Days Supply; Dollar Amounts.

Physician and Facility Claims Data: Member Identifier; Physician or Facility Identifier; Procedures (CPT-4, revenue codes, ICD-9); Diagnosis (ICD-9-CM, DRG); Admission and Discharge Dates; Date and Place of Service; Dollar Amounts.

Lab Test Results Data: Member Identifier; Lab Test Name; Result.

Consumer Elements: Member Identifier; Income; Net Worth; Education; Race and Ethnicity; Life Stage; Life Style Indicators.

A ballpark cost estimate of providing a data file to NHTSA that includes 40,000 patients with two years of data is $50,000.

The database contact in this task indicated that E-codes are indeed captured, and it is much more common for them to be coded using 4 digits rather than 3. A "quick and dirty" run of the database (excluding the recent additions from Ovations and Pacific Care) identified 126 members age 65+ with 4-digit E-codes in the range of E8130 to E8139 (motor vehicle traffic accident involving collision with other vehicle). It was noted, however, that this older population group is increasing in the database as a result of bringing more Medicare Part D members into the plans that supply Ingenix with data. In summary, the Ingenix LabRx database appears to have the necessary elements for use in future NHTSA studies on medications and crash risk.

The Centers for Education and Research on Therapeutics

The Centers for Education and Research on Therapeutics is a research program administered by the Agency for Healthcare Research and Quality, in consultation with the Food and Drug Administration, within the U.S. Department of Health and Human Services. The mission of the CERTs is to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products.[11] There are seven CERTs centers, each with the following emphasis:

- Duke University Medical Center (therapies for disorders of the heart and blood vessels);
- HMO Research Network (drug use, safety and effectiveness studies in HMO populations);
- University of Alabama at Birmingham (therapies for musculoskeletal disorders);
- University of Arizona Health Sciences Center (reduction in drug interactions that result in harm to women);
- University of North Carolina at Chapel Hill (therapies for children);
- University of Pennsylvania School of Medicine (therapies for infection and antibiotic drug resistance); and
- Vanderbilt University Medical Center (prescription drug use in a Medicaid population).

An e-mail request was sent to the director of pharmaceutical studies at the Agency for Healthcare Research and Quality regarding the feasibility of using CERT databases for future NHTSA research. At the time this chapter was developed as a project interim report in 2006, no contacts had been received. In parallel with requests made at the administrative level within CERTs, a request was made to a particular CERTs center, the HMO Research Network. A summary of the results of this contact follows.

HMO Research Network

The CERTs HMO Research Network comprises the investigators, information resources, delivery systems, and the following health maintenance organizations that are committed to public domain research (www.certs.hhs.gov/centers/hmo.html):

- Harvard Pilgrim Health Care, Boston, MA;
- Meyers Primary Care Institute/Fallon Community Health Plan, Worcester, MA;
- Group Health Cooperative of Puget Sound, Seattle, WA;
- HealthPartners Research Foundation, Minneapolis, MN;
- Kaiser Permanente Georgia, Atlanta, GA;

[11] Visit www.certs.hhs.gov

- Kaiser Permanente Northern California, Oakland, CA;
- Kaiser Permanente Northwest, Portland, OR;
- Kaiser Permanente Colorado, Denver, CO;
- Kaiser Permanente Hawaii, Honolulu, HI;
- Kaiser Permanente Southern California, Pasadena, CA;
- Lovelace Clinic Foundation, Albuquerque, NM;
- Henry Ford Health System – Health Alliance Plan, Detroit, MI;
- Scott and White Health System, Temple, TX; and
- Marshfield Clinic Research Foundation, Marshfield, WI.

The HMO Research Network focus is on use, safety, and effectiveness studies of therapeutics using health plans for defined populations. Key projects include patient interventions to increase adherence to beta blocker therapy after heart attack; working with the FDA to develop new methods for rapid discovery of adverse drug reactions; and assessing medication errors in ambulatory cancer care.

The principal investigator of the HMO Research Network served as the contact for our request. He indicated that the center has considered research like this over the years, and concluded that health plan records were probably unable to satisfactorily identify the operators of vehicles involved in motor vehicle accidents. The studies of which he is aware use motor vehicle registry data to identify the individuals of interest, and then they link this information to health plans' data on drug exposures and other conditions. He stated that he didn’t know of any reason the health plan records would have improved in this regard. So, the participation of the HMO Research Network would require developing a linkage agreement with relevant motor vehicle registries. He also indicated that the HMO CERT often collaborates with external investigators, but doesn't work as a data vendor.

Based on the information provided by the HMO CERT, this database is not recommended for future data mining activities by NHTSA.

Discussion and Recommendations

This research has contributed evidence that can help guide continuing investigations into the relationship between (multiple) medication usage and driving safety. Such studies will provide the knowledge base upon which to develop and implement new programs to inform key health care providers,[12] and consumers themselves, about specific drugs and combinations of drugs that place (older) adults at greatest risk when they drive. The proliferation of poly-pharmacy among older people who remain frequent, active drivers—including not only a wide range of potentially driver-impairing (PDI) medications, but also drugs on the Beers list of inappropriate medications for older adults—only underscores the need for such educational countermeasures. To that end, this pilot study has provided an update on the prevalence of prescription medications in the older population, and the effects on driving of specific drugs/drug classes. In addition, its results point to what appear to be relatively stronger, and weaker, strategies for carrying out future work in this vital area of research.

The literature review in this project updated the information presented in *Identifying Strategies to Study Drug Usage and Driving Functioning Among Older Drivers* (Lococo & Staplin, 2006). Relevant reports were identified by monitoring summaries of recently published research on medication usage, injury data, and other variables bearing on the relationship between PDI medications and driving, that were posted in the SafetyLit database between October 2005 and October 2007. This service regularly examines more than 2,600 scholarly journals from fields including education, engineering specialties, ergonomics, law and law enforcement, medicine, physiology, psychology, public health, public safety, nursing, social work, and traffic safety. This report presents a number of new findings identified in this manner. Specifically, new information is reported about the effects on driving of an anti-seizure medication (topiramate); acute and stable dosing of opioids; sedating and non-sedating antihistamines; antidepressants; short and long half-life sedative-hypnotics; an immediate-release versus extended-release anti-anxiety medication (benzodiazepine); a skeletal muscle relaxant (carisoprodol); and anti-diabetic medications.

The current review of the technical literature also provided insight into the risk associated with chronic medical conditions versus the effects of the medications that treat these conditions. This question was examined in the context of studies bearing on the risk of falls; there is evidence that the same medications that mediate falls risk, may also mediate motor vehicle crash risk. What emerges in this review is that some geriatric patients experience an increased risk of falling due to cardiovascular adverse effects of sedatives, antihypertensives, and other medications, and that when these fall-risk-increasing-drugs are withdrawn there is a resulting, persistent benefit — a significant reduction in the occurrence of falls (Van der Velde et al., 2007). At the same time, researchers have found that chronic medical conditions were often more important than medications in causing falls in high-functioning community-dwelling older people (Lee et al., 2006).

At least two recommendations are warranted by these results. First, an ever-expanding volume of work in this area makes it fruitful for NHTSA to sponsor future, periodic updates to

[12] For example: NHTSA's "Pharmacist Education—Medication Impaired Driving" has produced an ACPE-approved curriculum to foster increased interaction with older consumers about drugs and driving safety.

remain current with new research. Also there are likely to be safety benefits for many older people from an individualized medication review by their pharmacist, with physician follow-up, that may lead to the withdrawal of selected medications, for selected conditions, and/or their replacement with alternative prescriptions without known PDI (or fall-risk-increasing) effects.

Next, the efficacy of data-mining using large, patient-level administrative databases was highlighted in this project. Ideally, such a database would contain linked medical, hospital, and pharmaceutical data for each eligible person, and, ideally, would be the *only* provider of services. All prescriptions obtained would be through the insurance provider, so that a complete record of drug utilization would be captured in the claims database. Data fields would include dates of inpatient and outpatient hospital and doctor services; diagnosis codes to document the reason for the healthcare visit, including E-codes with 4 digits to indicate external causes of injury for all diagnoses (so claims resulting from a motor vehicle cash may be identified, and the injured person may be identified as either the driver or a passenger); patient demographics, including date of birth/age, gender, and zip code of residence; and comprehensive pharmacy data.

While this ideal database does not presently exist, several promising candidates for future NHTSA investigations were identified. One such candidate is the Ingenix LabRx database (United Healthcare). Four-digit E-codes are captured in this database, including codes in the range of E8130 to E8139 (motor vehicle accident involving collision with other vehicle); and, the number of older people in the database is increasing as a result of bringing more Medicare Part D members into the plans that supply Ingenix with data. The estimated cost of providing a file to NHTSA that includes 40,000 patients with two years of relevant data is $50,000.

Another candidate that may be recommended is the Veteran's Health Administration Pharmacy Benefits Management Database. According to French, Campbell et al. (2006), the data available through the VHA system allows one to study the association between a particular drug and an injury or adverse event by identifying a population at risk and then linking outpatient medications with healthcare utilization in that population. There are 8 million veterans nation-wide who use the VA for health care. Of this group, over 5.1 million get their prescriptions from inside of the VA system. Many are over the age of 65. Motor vehicle crashes are coded in the VA database. While drivers and passengers are not separately identified, the database contains ICD-9-CM E-codes; the 4th digit identifies the injured person as a passenger or driver. This database is a nomenclature-based database, so exact drug names, rather than drug codes are included; the exact drug names can be easily matched to NDC codes, however. One potential drawback is that the VHA/PMB has been historically proprietary, and can only be used by non-VA researchers if a collaborative agreement were made with an investigator within the VA. For the VA to release data for a traffic safety study as presently contemplated, NHTSA and its researchers would need to identify the needed information and provide an analysis plan to the VA IRB, which would review the request. They would only provide the data to the VA principal investigator or a research member who is affiliated with the VA. If the request is approved, the cost for data and data cleaning—but not the actual data mining analyses—for a study population of 40,000 would cost approximately $30,000.

The data mining exercise undertaken in this research consisted of a set of exploratory analyses in a proprietary database that is the property of NHTSA, the PharMetrics Patient-Level Database developed through a prior contract (LeRoy & Morse, 2005). The main objectives were

to refine our understanding about the exposure of seniors to PDI prescription medications, and to prioritize specific combinations of these drugs for subsequent field study. This database consists of cases and controls—individuals with and without motor vehicle crash involvement—who have been continuously enrolled for 6 months or more in prescription medication insurance plans. It includes E-codes identifying causes of injury, plus entries for patient demographics, number of medications dispensed, combinations of medications, and disease prevalence. A subset of 22,574 cases (versus 100,557 controls) was considered in the present analyses.

The range of driver ages encompassed in this exercise included 16-49, then 5-year cohorts through age 74, and 75+. The number of PDI drugs taken by individuals in the study population ranged from zero to 16. These analyses revealed that the rate of use of multiple PDI medications by crash-involved drivers climbs steadily with age, until leveling off at the 65- to 69-year-old cohort. It was also interesting to note that from one-third to one-half of crash-involved drivers in each cohort older than 50 were taking no PDI medications at all.

In the context of the present project, the key findings of this data mining exercise were a set of 2-PDI drug combinations to serve as inclusion criteria in the subsequent field study. Based on the prevalence of specific combinations of medications among drivers 65 and older in the PharMetrics database, a primary focus on medications to lower blood pressure (hypotensives) was recommended. Specifically, it was recommended that the pilot study should attempt to examine the effects on driving performance of this drug class in combination with one or more other classes of PDI medications – lipotropics, beta blockers, calcium channel blockers, NSAIDS, SSRIs, and gastric acid secretion reducers.

The field study conducted in this project included 44 generally healthy individuals recruited from residential communities in Delaware and Maryland, ranging in age from 57 to 89, who drove an average of 50 miles and/or three days each week. Data collected for this sample included medication usage—via one-on-one medication reviews with a visiting pharmacist—plus functional status information using a computer-based battery of measures validated as significant at-fault crash predictors in previous NHTSA research (see Staplin, Gish, & Wagner, 2003). Next, driving performance measures were collected, including an on-road evaluation by an occupational therapist/certified driver rehabilitation specialist (OT/CDRS) and brake response time measures, using an instrumented vehicle. For a subsample of 5 individuals, video, GPS and speed recordings in their own, private cars were also carried out to examine the variability in selected behaviors—surrogates of driver attention/distraction, plus speed choice—during independent driving versus drives with the OT, under comparable conditions.

Considerable difficulties were encountered in recruiting the research sample, with eventual success realized principally due to the generous support of management and staff at the participating residential communities. Attempts to relate observed differences in functional (cognitive) status, driving evaluation outcomes, and brake response time to medication usage, via stepwise logistic regression, were similarly challenging, and ultimately unproductive due to the small sample size relative to the number of drugs and drug classes used as predictors in the linear model. None of the differences in outcome measures, even when coded only as binary (e.g., pass/fail) variables, were significantly predicted by any particular drug combination represented in the study sample. In retrospect, this result might have been anticipated, given that all sample members were selected according to common and fairly narrow entry requirements.

A descriptive summary of these data indicated that the small subset (4) of drivers who "failed" the OT evaluation also were among the oldest. This may be explained by the fact that PDI medications are more impairing to driving performance with increasing age, due to a wide range of (age-related) physiological changes and changes in how these drugs are metabolized (see Herrlinger & Klotz, 2001). The descriptive data summary also suggested that ACE inhibitors, generally, and ACE inhibitor/thiazide diuretic combinations, in particular, may be deserving of special attention in future research; but this must be regarded as a tentative conclusion given the research limitations noted above.

The analyses of behavioral variability during independent driving versus a formal driving evaluation, based on instrumented vehicle data, were more revealing. A case study with an 82-year-old showed that, while speed choice was often lower when driving independently than during the driving evaluation, on those specific road segments that were common to both sets of drives and which had the lowest traffic volumes – and therefore the fewest constraints on drivers' speed choice – this sample member was more likely to drive *faster* on her own than when observed by the OT.

Analysis of continuous driver face and external road view video recordings compared glance direction – an indicator of driver attention – for both types of driving, and found that for five sample members, in the aggregate, there was more time spent looking down and inside the vehicle and less looking toward the inside rearview mirror when driving independently. And, this trend was more pronounced during intersection negotiation, even when the driver was not in car-following mode – in other words, when active scanning of the road environment is critical. The apparently greater willingness of study participants to devote attention to locations inside the vehicle during intersection negotiation – though still a small percentage of their overall glance distributions – highlights a difference between independent driving and (older) peoples' behavior during a driving evaluation that may have significant safety implications.

The field study results indicate that small-sample empirical investigations are not likely to be the most practical route to a better understanding of (multiple) medications and driving impairment. Not only will the prevalence of PDI drugs in any population-based sample work against successfully modeling the predictor-criterion relationships of greatest interest, but—based on experience in this project—sample recruitment will be daunting without a high level of support and assistance from others who are already familiar to and trusted by the prospective research participants.

Two other research methods explored in this pilot project may be much more strongly recommended. First, data mining in large administrative claims databases with patient-level information holds a clear promise for pinpointing the most problematic drugs and combinations of drugs to target in future information and education interventions; specific candidate databases are highlighted in this report. Also of potentially great value are new studies utilizing miniature in-car instrumentation, integrating affordable off-the-shelf technology to unobtrusively monitor the behavior of (consenting) drivers. Measures of behavioral variability as a function of driving context, as well as normative exposure data long sought as the denominator by traffic safety analysts, may realistically be expected to result from such investigations.

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APPENDICES

Appendix A

SAMPLE PARTICIPANT RECRUITMENT MATERIAL

IRB approval #06-0248, Univ. of North Carolina, Chapel Hill, Office for Human Research Protection

DO YOU DRIVE SEVERAL TIMES A WEEK?
JOIN A FIRST-OF-ITS-KIND RESEARCH STUDY!

This is an opportunity to support the National Highway Traffic Safety Administration develop educational materials for older drivers who are taking prescription medications for high blood pressure, high cholesterol, heart conditions, diabetes, and many other common medical conditions.

Men and women who hold a valid license and routinely drive 3 or more days per week are asked to join a research study. Other eligibility requirements are:

1) **You have been taking a prescription medication for high blood pressure for three months or longer. Of special interest are the 'ACE Inhibitor' type drugs. Some common brand names for these medications are:** *Prinivil, Zestril, Altace, Zestoretic, Prinzide, Vaseretic, Vasotec, Accupril, Lotensin,* and *Monopril.*
2) **You are also taking a prescription medication for *any* of the following conditions: *depression, thyroid deficiency, gastric acid reflux, high cholesterol, chronic pain or inflammation*.**
3) **You have NOT been involved in more than 2 crashes serious enough to be reported, in the past 5 years.**
4) **You do NOT have epilepsy or another seizure disorder that can cause you to lose consciousness.**

Approximately three hours of your time will be needed, over a period of 1 or 2 months. You will receive a free consultation with a pharmacist about the medications you are taking. You will also receive a professional driving evaluation by a Certified Driving Rehabilitation Specialist, at no charge. And, you may be asked to drive according to your normal habits for a week with instruments in your car that record how and where you drive.

ALL DATA FROM THIS STUDY WILL BE ABSOLUTELY CONFIDENTIAL. ONLY GROUP STATISTICS – NO INDIVIDUALS – WILL BE INCLUDED IN THE STUDY RESULTS. YOUR LICENSE WILL NOT BE AFFECTED IN ANY WAY.

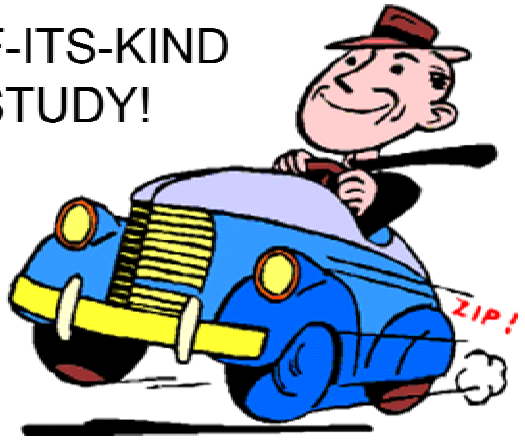
A $100 payment is offered for research participants who qualify. If interested, please contact [redacted] (toll free number).

By joining this research study you will help others drive more safely.

This study has been approved by the UNC Institutional Review Board, IRB # 06-0248.

DO YOU DRIVE SEVERAL TIMES A WEEK?

JOIN A FIRST-OF-ITS-KIND RESEARCH STUDY!



This is an opportunity to support the National Highway Traffic Safety Administration develop educational materials for older drivers who are taking prescription medications for high blood pressure, high cholesterol, heart conditions, diabetes, and many other common medical conditions.

Men and women age 55+ who hold a valid license and drive 3 or more days (or 50 miles) per week are eligible to join a research study. Other requirements are:

1) You have been taking a prescription medication for high blood pressure for three months or longer. Of special interest are the 'ACE Inhibitor' type drugs. Some common brand names for these medications are: Prinivil, Zestril, Altace, Zestoretic, Prinzide, Vaseretic, Vasotec, Accupril, Lotensin, and Monopril.

2) You are also taking a prescription medication for any of the following conditions: depression, gastric acid reflux, high cholesterol, chronic pain or inflammation.

3) You have not been involved in more than 2 crashes serious enough to be reported, in the past 5 years.

4) You do not have epilepsy or another seizure disorder that can cause you to lose consciousness.

ALL DATA FROM THIS STUDY WILL BE *ABSOLUTELY CONFIDENTIAL.*
ONLY GROUP STATISTICS – NO INDIVIDUALS – WILL BE INCLUDED IN THE STUDY RESULTS.
YOUR LICENSE WILL *NOT* BE AFFECTED IN ANY WAY.

A $100 payment is offered for research participants who meet the eligibility requirements. A medication review by a registered pharmacist will also be provided, at no charge.

The study location will be the Cokesbury Village CCRC in Hockessin, DE.

If interested, please contact Pat Alderson, Rehab Services Manager, at 235-6076.

Approximately three hours of your time will be needed, over a period of 1 or 2 months. You will be asked questions about the medications you are taking, and about your driving habits. You will receive a professional driving evaluation by a Certfied Driving Rehabilitation Specialist at no charge. And, you will be asked to drive according to your normal habits for a week with instruments in your car that record how and where you drive.

Appendix B

REASONS FOR NOT PARTICIPATING SURVEY

Did you receive the flyer asking you to join the medications-and-driving study?

You may recall that flyers were distributed earlier this year, asking for older persons who are active drivers to join a study sponsored by the National Highway Traffic Safety Administration. We want to thank those residents who agreed to participate, and learn why others decided not to join this research effort. Please read the following statements and check all that apply to you.

"I did not participate in this study because:

__ I did not qualify for the study based on the medications I am taking."
__ I do not drive enough to qualify for the study."
__ I was out of town."
__ I was too busy; I did not want to commit to the time required for study participation (3 hours)."
__ I did not feel the incentive payment ($100) offered for study participation was enough."
__ I did not want to reveal my medication usage or medication history."
__ I did not want to drive with a stranger (for the driving evaluation part of the study)."
__ I did not want to drive an unfamiliar car (for the driving evaluation part of the study)."
__ I did not want instrumentation that would record my driving behavior to be installed in my car."
__ I did not trust that the results of my driving evaluation would remain confidential."
__ I was worried that the results of my driving evaluation would be reported to the DMV."
__ of reasons other than those listed above." (Please explain below.)

_____
_____
_____
_____

We appreciate your anonymous feedback. Please return this sheet to [redacted].

Appendix C

SAMPLE MEDICATION REVIEW FORM

Client Name: Xxxxxx Xxxxx **Age:** 82
Address: Xxxxxxxxxx
Phone: xxx-xxx-xxxx
Date of Visit: July 27, 2007
Referral: UNC Driving Study
Source of Information: patient

CC/HPI: This is a medication review that is part of a driving study.

PMH: XX is an 82 yr old woman who notes that she is being treated for high cholesterol, h/o stroke in 1999/2000 and high blood pressure. She notes she is very active in various activities such as working out about 3-4 times a day.

Medical Provider: Dr. X

Pharmacy/Insurance: Mail order via Express Script

Allergies: Nosebleeds with aspirin

Medications:

Plavix	Stoke Prevention (anticoagulant)	75mg	1 tablet once daily	Dr. X
Fosinopril	High Blood Pressure (ACE inhibitor)	10mg	1 tablet once Daily	Dr. X
Simvastatin	High Cholesterol (HMG coA reductase inhibitor)	10mg	1 tablet once daily in the evening	Dr. X
Glucosamine/Chondrotin	Arthritis	750mg/600mg	1 tablet once daily	Dr. X
B complex	Health Maintenance		1 tablet once daily	Dr. X
Calcium and Vitamin D	Bone Health	600/200	1 tablet twice daily	Dr. X
Tylenol	Arthritis (analgesic)		As needed	

Review of Systems: unremarkable except for a nosebleed last week which she attributes to the dry environment.

Recommendations:
1) Medication management: pt appears to be appropriately managing her medications and monitors for effectiveness by having her weight and blood pressure checked at the health club. Her medication regimen is appropriate for her history and there are no clinically significant interactions occurring.

Follow-up:
Will be followed up by Xxxx Xxxxx, OT for driving evaluation.

Work-up done by:
Xxxxx Xxxxx, PharmD, CGP, BCPP

Appendix D

SAMPLE ON-ROAD DRIVING EVALUATION FORM

Identifier: (m/f, birth year, first & last initial)_____

Date _____ Time _____ Evaluator _____

Valid License: YES/verified Road Conditions: _____

What medications have you taken in the last 12 hours? _____
_____
_____

What is your past medical history? _____
_____
_____
_____

Substance use history _____
_____
Driving History/Record/Restrictions?_____
_____

Behind the Wheel Driving Performance:

Key: ✔ = performs consistently and independently, very minor errors do not compromise safety
*** =** performed task/skill adequately but comment is added as a qualifier
– = single error or performs inconsistently, 25-75% of available opportunities, pattern of errors may indicate that safety is compromised
X = requires physical or verbal instructor intervention to manage hazards or prevent crash, performs less than 25% of available opportunities

Vehicle Entry

_____manages key to open and close the door
_____properly positions self in the driver's seat
_____secures any mobility aides
_____adjust seat
_____adjusts mirrors
_____fastens seatbelt
_____accommodates and adjusts to vehicle; understands the usual placement of the turn signal, can manage the column shift, looks for symbols for P, R, N, D)
Comments: _____
_____

Initiating Driving/Starting Procedures

_____turns key to start
_____depresses brake prior to shifting gears
_____shifts to proper gear
_____checks mirrors
_____checks blind spots
_____signals intent
_____applies accelerator/brake as appropriate
_____ demonstrates intact "practical" brake reflexes
Comments: _____
_____

General Driving

_____accelerates gradually
_____brakes smoothly
_____maintains consistent speed appropriate to area and road conditions
_____on roadways that do not have lane markings, keeps right position in preparation for/potential of oncoming vehicles
_____on roadways that have lane markings, maintains lane position, does not drive on or cross lane lines left, does not hit or near curb or right lane markings
_____ in travel lane, maintains central path of travel, alters path in response to obstacles (bicyclers, pedestrians, potholes, speed bumps, other vehicles etc.)
_____anticipates other vehicles and hazards
_____signals intent for lateral maneuvers in sufficient time frame
_____performs lane changes at an appropriate place
_____cancels signal after lane changes
_____yields right of way
_____demonstrates awareness of posted speeds and looks for signs
_____ maintains appropriate space cushion for speed of travel
_____ alters speed of travel for potential hazards (fast moving side vehicles, pedestrians, bicyclers, speed bumps, potholes/road debris etc.)
_____regularly uses rearview and side view mirrors to note traffic to the rear and sides
_____checks blind spots via mirrors and head checks for merges and lane changes
_____completes organized process for lane changes (look, signal, headcheck, move, recheck traffic)
Comments: _____
_____

Controlled Intersections (traffic light or stop sign, with/without specified turn lanes)

_____anticipates traffic lights/stop sign
_____positions vehicle in appropriate lane
_____respects pedestrian crosswalk
_____comes to a complete stop as req'd-stops at/before the stop line or stop sign
_____checks for oncoming traffic from right, left, and straight ahead
_____correctly manages amber light
_____observes "no turn on red"
_____proceeds when safe and indicated
_____understands right of way issues at 2, 3, 4, way stop intersections and yields right of way as required

Comments: _____
_____

Uncontrolled Intersections

_____despite lack of intersection control, recognizes the need to slow and search for traffic and potential hazards
_____ anticipates other vehicles/pedestrians
_____ yields right of way
_____ proceeds when indicated

Comments: _____
_____

Turns (those with/without a designated turn lane or specific turn signal)

_____chooses and makes the turn from the appropriate lane
_____signals intent
_____yields to oncoming traffic
_____checks blind spot prior to turning
_____coordinates speed through the turn, accelerates out of the turn
_____coordinates upper extremities for steering
_____allows recovery of steering wheel
_____corrects for over steering wheel as needed
_____maintains lane position through turn
_____understands time and space requirements for unprotected left turns (judges traffic for appropriate amount of space and drives at speed necessary to safely move across and turn in with traffic)
_____understands time and space requirements for unprotected right turns (judges traffic for appropriate amount of space and drives at speed necessary to safely turn in with traffic)

Comments: _____
_____

Visual Skills

_____recognizes color of traffic light
_____notes and responds to arrow signals
_____reads speedometer or understands the relative placement of the arrow/needle to the speed
_____reads large regulatory signs-speed limit, no turn on red, construction etc.
_____recognizes that the road bends or curves and moves smoothly through them
_____recognizes and avoids road dividers, islands or curbs
_____has 20-30 second forward scan allowing for anticipation of road issues
_____uses ground scan to note lane markings, arrows, directions for parking lots, cues from other cars etc.
_____uses mirrors, completes head check for blind spots
_____anticipates areas of limited space or the need to change lanes
_____follows lane markings
_____observes warning signs as demonstrated by an appropriate adaptive response or comment
_____notes and obeys stop signs or other traffic controls
Comments: _____
_____

Lot Parking

_____approaches the parking space in the appropriate lane
_____checks for traffic in the rear
_____signals intent
_____stops in appropriate spot
_____places foot on brake prior to changing gears
_____checks rear window, mirrors, front bumpers etc. when backing up
_____maneuvers vehicle into designated space) selects gears, steers in correct direction)
_____accurately judges distances to curb and other vehicles
_____avoids obstacles
_____centers the car in the parking space
Comments: _____
_____

Overall Comments/notes:_____
_____
_____

General Rating:
Good driver/no concerns
Adequate driver/few potential problem/driving habits
Fair Driver/lacks numerous good driving habits
Concerns about driving

Instructor intervened for:

_____ braking	Other: _____
_____ steering	_____
_____ speed	_____
_____ lane position	_____

How familiar are you with the major roads on which you traveled during your driving evaluation today? (please circle a number on the scale below)

very **un**familiar = 1 2 3 4 5 6 7 = very familiar

In your normal driving habits, how often do you drive on the major roads on which you traveled during your driving evaluation today? (please circle a number on the scale below)

very rarely = 1 2 3 4 5 6 7 = very often

When is it convenient for the research team to add the equipment into your vehicle? _____
What type of car will you be driving? _____
What number can you be reached to coordinate this installation? _____

SUGGESTIONS:

_____ M.S.,OTR/L, CDRS

_____DATE

Appendix E

COMBINED MEDICATION CLASSES FOR ANALYSIS

Medication Classes Per Pharmacist Review. (1=PDI Drug Class, 2= Non-PDI Drug Class)

			Non-PDI Other										PDI-Other															Vitamines/ minerals/ supplements						Sedating Antihistamine			PDI Eye Preparations			Antidepressants/ Antianxiety				NSAID	Anti-spasmodics GU	Cholesterol Lowering		Gastric Acid Secretion Reducer			Osteoporosis			Neurologic					Antidiabetic					Anti-Platelet/ Anticoagulant			Antihypertensive Diuretics				Antihypertensive Non Diuretic						Subject ID/Drugs	
Non-PDI Count	PDI Count	Count - All	OTC Antifungal Topical	OTC Antiflatulant	OTC Saline Nasal Spray	OTC Eye Tears	OTC Laxitive	OTC Cough Drops	OTC Topical Analgesic	OTC Analgesic	Nasal Spray Anticholinergic	Antihistamines Non Sedating	5 Alpha Reductase Inhibitor	Topical Antibiotic	Hormone Replacement Topical Cream	Phospho-diesterase 5 Enzyme Inhibitor	Inhaled Steroid	Bete Adrenergic Agents	Corticosteroid	Nasal Spray / Steroid	Antibiotic	Opiate Agonist	Narcotic Analgesic	Thyroid Supplement	CNS Stimulant / ADHD	Aromatase Inhibitor	Antiarrhthmic	OTC / Eye Supplement	OTC / Joint Supplement	OTC / Fish Oil Supplement	OTC / Herbal	OTC Vitamin/ Mineral	Potassium Supplement	Nasal Spray / Antihistamine	OTC Antihistamine / Sedating	OTC Analgesic Antihistamine	Immuno-modulator / Dry Eyes	Steroid Eye Drops	Glaucoma Drops	SSRI	SNRI	Anti Anxiety Non BZD	Benzodiazepine	NSAID	Antispasmodics GU	Antilipemic	HMG Coa Reductase Inhibitor	Proton Pump Inhibitor	OTC H2 Blocker	OTC Antacid	Selective Estrogen Receptive Modulator	Bisphosphonate	Calcitonin Hormone	Dopamine Agonist	Cholinesterase Inhibitor	Anti Convulsant	Anti Mania	Antipsychotic	Dipeptidyl peptidase 4	Thiazolidine	Alpha Glucosidase Inhibitor	Biguanide	Sulfonylurea	Antiplatelet	Anticoagulant / Coumadin Type	OTC Antiplatelet	Combination Diuretic	Thiazide Diuretic	Potassium Sparing Diuretic	Loop Diuretics	Angiotensin II Receptor Antagonist	Combo Calcium Channel Blocker - ACE Inhibitor	Calcium Channel Blocker	ACE Inhibitor	Beta Blocker	Alpha 1 Adrenergic Blocker	Age	DriverID
1	4	5																														2															1															1	1										1			57	f50bn
0	0	0																																																																													65	f42bf
5	3	8								2																				2		2									1											2				1										2								1			68	f39mw
4	12	16				2	2																1	1								2					1									1	1	1				2														1					1	1		1	1	1		69	f38bb
3	10	13																						1	1				2			2									1				1	1	1							1			1										2								1	1		69	f38eg
4	6	10										2																				2	2											1			1												1			1			2	1						1				69	f38ad
3	8	11	2									2																				2												1		1	1													1	1							1					1	1			71	f36ah
3	7	10								2											1											2							1							1	1																			2				1		1			1		72	f35kw
6	5	11													1				1								2	2	2	2	2		1												1																				2										1	73	m34gs
1	5	6																																											1	1																		1	2	1						1				75	m32jf
5	6	11								2																				2		2							1							1	1	1			2															2	1				1						76	f31ij
0	0	0																																																																													76	m31tp
6	5	11																									2	2	2	2	2							1					1			1																			2		1			1						76	f31is
8	12	20		2			2						1								1			1					2	2		2										1					1	1	1			2	2			1	1	1						1		2								1			76	m31ms
6	9	15						2	2	2		2					1	1			1	1					1			2			2												1		1																			1								1				76	f31mm
4	3	7																										2			2															1				2															2		1							1		77	f30aw
1	8	9													1									1								2													1			1																	1				1				1	1			78	f29cm
7	8	15		2	2	2				2	2			1						1	1												2		1													1	1			2																	1						1			79	f28sg
5	4	9																						1					2			2	2														1					2														2				1					1		79	f28eh
3	8	11											1	1																		2													1		1				2											1			2		1						1		1	80	m27gm
2	4	6																														2														1	1							1											2							1				80	m27ff
2	3	5																														2												1			1																		2					1						80	f27lh
6	7	13				2	2			2		2																				2			1								1	1			1	1																	2		1			1						80	m27rc
5	4	9				2					2																		2			2															1	1																	2		1							1		81	m26hb
6	6	12					2			2																		2				2			1								1					1		1		2															2		1			1						81	f26jc
2	4	6																														2															1																		2		1			1		1				81	m26cq
3	3	6								2																			2			2															1																1										1			82	f25ml
1	0	1								2																																																																				82	f25aj
2	8	10					2																								2				1							1	1			1	1																						1	1		1			82	f25js
2	5	7																														2			1								1			1		1																2	1										83	m24wt
3	9	12																											2		2							1					1		1													1		1		1		2		1			1				1		83	m24lh
2	5	7																														2													1	1												2						1						1		1				83	f24gs
3	6	9				2	2			2																																		1		1													1			1		1									1			83	m24js
0	0	0																																																																													84	f23hm
2	8	10																						1							2				1										1	1																1		2		1			1		1				84	f23ch
3	3	6								2																					2														1																	1	2					1						85	m22pp
3	6	9																	1												2			1													1					2			1											2		1						1			85	f22vb
3	5	8					2														1											2														1	1	1																		2					1						85	f22sp
6	6	12																	1									2	2	2		2												1			1					2														2		1			1				1		85	f22pv
4	3	7					2																								2															1					2														2		1						1			86	m21er
3	4	7																											2			2															1	1		1																2										1	87	m20ru
1	3	4																																												1																				2								1	1		88	m19pb
3	8	11					2																1			1					2													1		1																1			2				1				1		1	88	m19mg
2	7	9																		1											2							1									1																1			2							1		1	1	89	m18rt
			1	2	1	5	9	1	1	11	2	4	2	2	1	1	1	1	1	3	5	2	1	7	1	1	1	4	11	7	2	37	2	2	4	2	1	1	3	1	2	1	3	9	5	10	34	15	2	2	3	8	2	1	1	3	2	1	1	4	1	2	6	4	7	30	4	14	1	4	14	2	11	16	10	5		Count

Medication Classes Taken on the Day of the OT Evaluation

(1=PDI Drug Class, 2= Non-PDI Drug Class)

			Non-PDI Other						PDI-Other											Vitamines/ minerals/ supplements						Sedating Antihistamine			PDI Eye Preparations		Antidepressants/ Antianxiety			NSAID	Anti-spasmodics GU	Cholesterol Lowering		Gastric Acid Secretion Reducer			Osteoporosis			Neurologic					Antidiabetic					Anti-platelet/ Anticoagulant			Antihypertensive Diuretics				Antihypertensive Non Diuretic						Subject ID	
Non-PDE Count	PDI Count	Count - All	Antihistamines Non Sedating	OTC Analgesic	OTC Laxitive	OTC Eye Tears	OTC Antiflatulant	5 Alpha Reductase Inhibitor	Antiarrhthmic	Thyroid Supplement	CNS Stimulant	Aromatase Inhibitor	Opiate Agonist	Antibiotic	Nasal Spray Steroid	Inhaled Steroid / Asthma	Corticosteroid	Topical Antibiotic	Hormone Repl. Topical Cream	OTC / Eye Supplement	OTC / Joint Supplement	OTC / Fish Oil Supplement	OTC / Herbal Supplement	OTC Vitamin/ Mineral	Potassium Supplement	Nasal Spray / Antihistamine	OTC Antihistamine / Sedating	OTC Analgesic Antihistamine	Immuno-modulator / Dry Eyes	Glaucoma Drops	SSRI	SNRI	Non BZD Anti-Anxiety	NSAID	Antispasmodics GU	Antilipemic	HMG Coa Reductase Inhibitor	Proton Pump Inhibitor	OTC H2 Blocker	OTC Antacid	Selective Estrogen Receptive Modulator	Bisphosphonate	Calcitonin Hormone	Dopamine Agonist	Cholinesterase Inhibitor	Anti Convulsant	Anti Mania	Antipsychotic	Dipeptidyl peptidase 4	Thiazolidine	Alpha Glucosidase Inhibitor	Biguanide	Sulfonylurea	Antiplatelet	Anticoagulant / Coumadin Type	OTC Antiplatelet	Combination Diuretic	Thiazide Diuretic	Potassium Sparing Diuretic	Loop Diuretics	Angiotensin II Receptor Antagonist	Combo Calcium Channel Blocker ACE Inhibitor	Calcium Channel Blocker	ACE Inhibitor	Beta Blocker	Alpha 1 Adrenergic Blocker	Age	DriverID
1	4	5																						2													1															1	1											1			57	f50bn
1	0	0																																																																	65	f42bf
4	3	7																				2		2								1										2				1										2								1			68	f39mw
4	11	15			2	2				1														2					1							1	1	1				2													1					1	1		1	1	1		69	f38bb
3	10	13								1	1										2			2								1			1	1	1							1			1									2								1	1		69	f38eg
4	6	10	2																					2	2									1			1													1			1			2	1						1				69	f38ad
1	7	8																						2												1	1													1	1							1					1	1			71	f36ah
2	7	9											1											2						1						1	1																			2				1		1			1		72	f35kw
6	4	10													1					2	2	2	2	2		1											1																			2										1	73	m34gs
1	5	6																																		1	1																		1	2	1						1				75	m32jf
5	6	11		2																		2		2						1						1	1	1			2															2	1				1						76	f31ij
0	0	0																																																																		76	m31tp
6	5	11																		2	2	2	2	2						1				1			1																			2		1			1						76	f31is
8	10	18			2		2			1											2	2		2									1				1	1	1			2	2			1	1	1						1		2								1			76	m31ms
3	6	9	2									1				1					2			2										1		1																			1								1				76	f31mm
4	3	7																			2			2													1				2															2		1							1		77	f30aw
1	8	9								1									1					2											1			1																	1				1				1	1			78	f29cm
2	7	9													1			1						2		1											1	1			2																	1						1			79	f28sg
5	4	9								1											2			2	2												1					2														2				1					1		79	f28eh
4	7	11						2										1						2												1		1				2											1			2		1						1		1	80	m27gm
2	4	6																						2													1	1							1											2							1				80	m27ff
2	2	4																						2													1																			2					1						80	f27lh
3	5	8			2																			2										1			1	1																		2		1			1						80	m27rc
3	4	7																			2			2													1	1																		2		1							1		81	m26hb
4	4	8																		2				2														1		1		2														2		1			1						81	f26jc
2	4	6																						2													1																			2		1			1		1				81	m26cq
2	3	5																			2			2													1																	1										1			82	f25ml
1	0	1		2																																																															82	f25aj
2	5	7			2																			2										1			1	1																							1			1			82	f25js
2	3	5																						2										1			1																			2	1										83	m24wt
3	9	12																				2		2							1				1		1													1		1		1		2		1			1				1		83	m24lh
2	5	7																						2												1	1												2						1						1		1				83	f24gs
1	6	7			2																														1		1													1			1		1									1			83	m24js
0	0	0																																																																		84	f23hm
2	8	10								1														2				1									1	1																1		2		1			1		1				84	f23ch
3	3	6		2																				2													1																		1	2					1						85	m22pp
3	4	7																						2			1																2			1										2		1						1			85	f22vb
3	5	8			2									1										2												1	1	1																		2					1						85	f22sp
6	6	12															1			2	2	2		2										1			1					2														2		1			1				1		85	f22pv
4	3	7			2																			2													1					2														2		1						1			86	m21er
3	4	7																			2			2													1	1		1																2										1	87	m20ru
1	3	4																																			1																			2								1	1		88	m19pb
3	8	11			2				1	1														2											1		1																1			2				1				1		1	88	m19mg
2	5	7																						2													1																1			2							1		1	1	89	m18rt
			2	3	8	1	1	1	1	7	1	1	1	1	2	1	1	2	1	4	11	7	2	37	2	2	1	1	1	3	1	2	1	7	5	10	34	14	1	2	3	8	2	1	1	3	2	1	1	4	1	2	6	4	7	30	4	14	1	4	14	1	11	16	10	5	Count	

Appendix F

ANVIL CODING MANUAL

Nodes	
G Group	---
I Group	---
T Group	
M Group	---

Generated by Anvil on Tue Nov 13 15:14:20 EST 2007

primary track

G.Glance

Where is the driver looking now? The default is looking **straight-ahead** (through the windshield). Code elements as:

Attributes

ValueSet (6 tokens)	**GlanceStatus**	---

Attribute Values

GlanceStatus

default	Straight ahead through the windshield
right+up	Right and up glance (e.g., rearview mirror); includes sharp eye cuts without a head turn, as well as head turns toward the inside rearview mirror
right only	Rightward only glance; includes sharp eye cuts to the right without a head turn, as well as head turns toward the right
left only	Leftward only glance; includes sharp eye glances to the left without a head turn, as well as head turns toward the left
down+inside	downward glance or apparent glance inside vehicle.
over shoulder	driver performs direct head check over shoulder (left or right)

primary track

I.Infrastructure

What are the significant aspects of the infrastructure? Default condition is driver traveling on continuous, unbroken section of roadway. Code elements as:

Attributes

ValueSet (7 tokens)	**InfrastructureStatus**	---

Attribute Values

InfrastructureStatus

default	continuous, unbroken section of roadway
intersection+stop	Intersections with stop signs. Begin at stop bar; end at other side of intersection
intersection with merge/yield	Merge locations at intersections with channelization and yield signs or merges at highway interchanges. Begin at stop bar in adjacent through lane; end at solid lane marking after turn/merge
intersection+signal	Intersections with traffic signals. Begin at stop bar; end on other side of intersection.
school/ped crossing	School crossing or other mid-block pedestrian crossing
railroad crossing	At-grade railroad crossing. Begin at stop line (if present) or just before tracks; end after tracks. Do not include area marked with advanced RRX signs or markings
parking lot	Parking lot or garage

primary track

T.Traffic

What is the level of attentional demand associated with other traffic? The default is no traffic in scene OR traffic in scene but far away or separated by a physical barrier. Code as follows:

Attributes

ValueSet (4 tokens)	**TrafficStatus**	---

Attribute Values

TrafficStatus

Default	No traffic in scene OR traffic in scene but is not an immediate threat (e.g., too distant or is separated by a physical barrier) OR is on an intersecting path removed from driver's current position.
Car following ONLY	Driver is following another vehicle (same lane or adjacent lane); potential for rear-end crash if not attending. NOTE: A leading vehicle is an immediate threat if it is within 4 seconds from the driver, which corresponds to an image size of 1/8 inch (3.2 mm) wide or larger.
Opposing traffic ONLY	Potential for head-on crash (but no car following/rear-end crash potential). NOTE: opposing approaching vehicles are an immediate threat as soon as they become visible in the driving scene (e.g., at a 5 sec preview distance), unless they are separated by a physical barrier.
Car following AND opposing traffic	Potential for rear-end crash and head-on crash.

primary track

M.Maneuver

What is the driver's maneuver? The default is **same path moving forward** Code elements as:

Attributes

ValueSet (7 tokens)	**ManeuverStatus**	---

Attribute Values

ManeuverStatus

Default	Same path moving forward
Left Turn	Driver turns left
Right Turn	Driver turns right
Lane Change	Driver changes lanes, either to the left or to the right
Overtaking/Passing	Driver overtakes/passes another vehicle
Backing	Driver performs a backing/reverse maneuver
Stopped	No vehicle movement

Appendix G

MEDICATION USE IN THE 12-HOUR PERIOD PRIOR TO THE OT EVALUATION, BY (1) OVERALL DRIVING EVALUATION SCORE, (2) UNALERTED BRAKE RESPONSE TIME QUARTILE, AND 3) LEVEL OF COGNITIVE DEFICIT.

MEDICATION USE IN THE 12-HOUR PERIOD PRIOR TO THE OT EVALUATION, BY <u>OVERALL DRIVING EVALUATION SCORE</u>.

Color coded according to OT Evaluation "Overall Score." Green = good driver/no concerns; blue = adequate driver/few potential problem/driving habits; yellow = fair driver/lacks numerous good driving habits; red = concerns about driving. 1=PDI Drug Class; 2=Non-PDI Drug Class

Subject ID		(row color)				Non-PDI Other						PDI-Other										
DriverID	Age		Non-PDE Count	PDI Count	Count - All	Antihistamines Non Sedating	OTC Analgesic	OTC Laxitive	OTC Eye Tears	OTC Antiflatulant	5 Alpha Reductase Inhibitor	Antiarrhythmic	Thyroid Supplement	CNS Stimulant	Aromatase Inhibitor	Opiate Agonist	Antibiotic	Nasal Spray Steroid	Inhaled Steroid / Asthma	Corticosteroid	Topical Antibiotic	Hormone Repl. Topical Cream
f50bn	57	Green	1	4	5																	
f42bf	65	Green	0	0	0																	
f39mw	68	Green	4	3	7																	
f38bb	69	Blue	4	11	15								1									
f38eg	69	Blue	3	10	13								1	1								
f38ad	69	Green	4	6	10																	
f36ah	71	Green	1	7	8																	
f35kw	72	Green	2	7	9											1						
m34gs	73	Green	6	4	10													1				
m32jf	75	Blue	1	5	6																	
f31ij	76	Green	5	6	11																	
m31tp	76	Blue	0	0	0																	
f31is	76	Green	6	5	11																	
m31ms	76	Blue	8	10	18								1									
f31mm	76	Green	3	6	9										1				1			
f30aw	77	Blue	4	3	7																	
f29cm	78	Blue	1	8	9								1									1
f28sg	79	Blue	2	7	9													1			1	
f28eh	79	Blue	5	4	9								1									
m27gm	80	Blue	4	7	11						2										1	
m27ff	80	Yellow	2	4	6																	
f27lh	80	Blue	2	2	4																	
m27rc	80	Green	3	5	8																	
m26hb	81	Blue	3	4	7																	
f26jc	81	Blue	4	4	8																	
m26cq	81	Green	2	4	6																	
f25ml	82	Green	2	3	5																	
f25aj	82	Green	1	0	1																	
f25js	82	Blue	2	5	7																	
m24wt	83	Yellow	2	3	5																	
m24lh	83	Green	3	9	12																	
f24gs	83	Blue	2	5	7																	
m24js	83	Red	1	6	7																	
f23hm	84	Blue																				
f23ch	84	Blue	2	8	10								1									
m22pp	85	Blue	3	3	6		2															
f22vb	85	Red	3	4	7																	
f22sp	85	Blue	3	5	8			2									1					
f22pv	85	Red	6	6	12															1		
m21er	86	Yellow	4	3	7			2														
m20ru	87	Green	3	4	7																	
m19pb	88	Yellow	1	3	4																	
m19mg	88	Red	3	8	11			2				1	1									
m18rt	89	Blue	2	5	7																	
Count						2	3	8	1	1	1	1	7	1	1	1	1	2	1	1	2	1

Subject ID	Vitamines/ minerals/ supplements						Sedating Antihistamine			PDI Eye Preparations		Antidepressants/ Antianxiety			NSAID	Anti-spasmodics GU	Cholesterol Lowering	
DriverID	OTC / Eye Supplement	OTC / Joint Supplement	OTC / Fish Oil Supplement	OTC / Herbal	OTC Vitamin/ Mineral	Potassium Supplement	Nasal Spray/ Antihistamine	OTC Antihistamine / Sedating	OTC Analgesic Antihistamine	Immuno-modulator / Dry Eyes	Glaucoma Drops	SSRI	SNRI	Anti-Anxiety Non BZD	NSAID	Antispasmodics GU	Antilipemic	HMG Coa Reductase Inhibitor
f50bn					2													1
f42bf																		
f39mw			2		2								1					
f38bb					2					1							1	1
f38eg		2			2								1			1	1	1
f38ad					2	2									1			1
f36ah					2												1	1
f35kw					2						1						1	1
m34gs	2	2	2	2	2		1											1
m32jf																	1	1
f31ij			2		2						1						1	1
m31tp																		
f31is	2	2	2	2	2						1				1			1
m31ms		2	2		2									1				1
f31mm		2			2										1		1	
f30aw		2			2													1
f29cm					2											1		
f28sg					2		1											1
f28eh		2			2	2												1
m27gm					2												1	
m27ff					2													1
f27lh					2													1
m27rc					2										1			1
m26hb		2			2													1
f26jc	2				2													
m26cq					2													1
f25ml		2			2													1
f25aj																		
f25js					2										1			1
m24wt					2										1			1
m24lh			2		2							1				1		1
f24gs					2												1	1
m24js																1		1
f23hm																		
f23ch					2				1									1
m22pp					2													1
f22vb					2			1										
f22sp					2												1	1
f22pv	2	2	2		2										1			1
m21er					2													1
m20ru		2			2													1
m19pb																		1
m19mg					2											1		1
m18rt					2													1
Count	4	11	7	2	37	2	2	1	1	1	3	1	2	1	7	5	10	34

Subject ID	Gastric Acid Secretion Reducer			Osteoporosis			Neurologic					Antidiabetic				
DriverID	Proton Pump Inhibitor	OTC H2 Blocker	OTC Antacid	Selective Estrogen Receptive Modulator	Bisphosphonate	Calcitonin Hormone	Dopamine Agonist	Cholinesterase Inhibitor	Anti Convulsant	Anti Mania	Antipsychotic	Dipeptidyl peptidase 4	Thiazolidine	Alpha Glucosidase Inhibitor	Biguanide	Sulfonylurea
f50bn															1	1
f42bf																
f39mw					2				1							
f38bb	1				2											
f38eg							1			1						
f38ad													1			1
f36ah													1	1		
f35kw																
m34gs																
m32jf																
f31ij	1			2												
m31tp																
f31is																
m31ms	1	1			2	2			1	1	1					
f31mm																
f30aw				2												
f29cm	1															
f28sg	1			2												
f28eh					2											
m27gm	1				2											1
m27ff	1							1								
f27lh																
m27rc	1															
m26hb	1															
f26jc	1		1		2											
m26cq																
f25ml																
f25aj																
f25js	1															
m24wt																
m24lh													1		1	
f24gs												2				
m24js													1			1
f23hm																
f23ch	1															
m22pp																
f22vb						2			1							
f22sp	1															
f22pv					2											
m21er					2											
m20ru	1		1													
m19pb																
m19mg																1
m18rt																1
Count	14	1	2	3	8	2	1	1	3	2	1	1	4	1	2	6

Subject ID	Anti-platelet/ Anticoagulant			Antihypertensive Diuretics				Antihypertensive Non Diuretic					
DriverID	Antiplatelet	Anticoagulant / Coumadin Type	OTC Antiplatelet	Combination Diuretic	Thiazide Diuretic	Potassium Sparing Diuretic	Loop Diuretics	Angiotensin II Receptor Antagonist	Combo Calcium Channel Blocker / ACE Inhibitor	Calcium Channel Blocker	ACE Inhibitor	Beta Blocker	Alpha 1 Adrenergic Blocker
f50bn											1		
f42bf													
f39mw			2								1		
f38bb		1					1	1		1	1	1	
f38eg			2								1	1	
f38ad			2	1						1			
f36ah					1					1	1		
f35kw			2				1		1			1	
m34gs			2										1
m32jf		1	2	1						1			
f31ij			2	1				1					
m31tp													
f31is			2		1			1					
m31ms	1		2								1		
f31mm		1								1			
f30aw			2		1							1	
f29cm		1				1				1	1		
f28sg					1						1		
f28eh			2				1					1	
m27gm			2		1						1		1
m27ff			2							1			
f27lh			2					1					
m27rc			2		1			1					
m26hb			2		1							1	
f26jc			2		1			1					
m26cq			2		1			1		1			
f25ml	1										1		
f25aj													
f25js								1			1		
m24wt			2	1									
m24lh	1		2		1			1				1	
f24gs		1						1		1			
m24js		1									1		
f23hm													
f23ch	1		2		1			1		1			
m22pp		1	2					1					
f22vb			2		1						1		
f22sp			2					1					
f22pv			2		1			1				1	
m21er			2		1						1		
m20ru			2										1
m19pb			2								1	1	
m19mg			2				1				1		1
m18rt			2							1		1	1
Count	4	7	30	4	14	1	4	14	1	11	16	10	5

Color coded according to OT Evaluation "Overall Score." Green = good driver/no concerns; blue = adequate driver/few potential problem/driving habits; yellow = fair driver/lacks numerous good driving habits; red = concerns about driving.

MEDICATION USE IN THE 12-HOUR PERIOD PRIOR TO THE OT EVALUATION, BY UNALERTED BRAKE REACTION TIME QUARTILE.

Color Coded According to Unalerted BRT: Red = slowest > 1356; Yellow=>1065 and <=1356; Blue = >877 and <=1065; Green = fastest <=877 1=PDI Drug Class; 2=Non-PDI Drug Class

Subject ID					Non-PDI Other						PDI-Other										
DriverID	Age	Non-PDE Count	PDI Count	Count - All	Antihistamines Non Sedating	OTC Analgesic	OTC Laxitive	OTC Eye Tears	OTC Antiflatulant	5 Alpha Reductase Inhibitor	Antiarrhythmic	Thyroid Supplement	CNS Stimulant	Aromatase Inhibitor	Opiate Agonist	Antibiotic	Nasal Spray Steroid	Inhaled Steroid / Asthma	Corticosteroid	Topical Antibiotic	Hormone Repl. Topical Cream
f50bn	57	1	4	5																	
f42bf	65	0	0	0																	
f39mw	68	4	3	7																	
f38bb	69	4	11	15			2	2				1									
f38eg	69	3	10	13								1	1								
f38ad	69	4	6	10	2																
f36ah	71	1	7	8																	
f35kw	72	2	7	9											1						
m34gs	73	6	4	10													1				
m32jf	75	1	5	6																	
f31ij	76	5	6	11		2															
m31tp	76	0	0	0																	
f31is	76	6	5	11																	
m31ms	76	8	10	18			2		2			1									
f31mm	76	3	6	9	2									1				1			
f30aw	77	4	3	7																	
f29cm	78	1	8	9								1									1
f28sg	79	2	7	9													1			1	
f28eh	79	5	4	9								1									
m27gm	80	4	7	11						2										1	
m27ff	80	2	4	6																	
f27lh	80	2	2	4																	
m27rc	80	3	5	8			2														
m26hb	81	3	4	7																	
f26jc	81	4	4	8																	
m26cq	81	2	4	6																	
f25ml	82	2	3	5																	
f25aj	82	1	0	1		2															
f25js	82	2	5	7			2														
m24wt	83	2	3	5																	
m24lh	83	3	9	12																	
f24gs	83	2	5	7																	
m24js	83	1	6	7			2														
f23hm	84	0	0	0																	
f23ch	84	2	8	10								1									
m22pp	85	3	3	6		2															
f22vb	85	3	4	7																	
f22sp	85	3	5	8			2									1					
f22pv	85	6	6	12															1		
m21er	86	4	3	7			2														
m20ru	87	3	4	7																	
m19pb	88	1	3	4																	
m19mg	88	3	8	11			2				1	1									
m18rt	89	2	5	7																	
Count					2	3	8	1	1	1	1	7	1	1	1	1	2	1	1	2	1

Subject ID	Vitamines/ minerals/ supplements						Sedating Antihistamine			PDI Eye Preparations		Antidepressants/ Antianxiety			NSAID	Anti-spasmodics GU	Cholesterol Lowering	
DriverID	OTC / Eye Supplement	OTC / Joint Supplement	OTC / Fish Oil Supplement	OTC / Herbal	OTC Vitamin/ Mineral	Potassium Supplement	Nasal Spray / Antihistamine	OTC Sedating Antihistamine /	OTC Analgesic Antihistamine	Immuno-modulator / Dry Eyes	Glaucoma Drops	SSRI	SNRI	Anti-Anxiety Non BZD	NSAID	Antispasmodics GU	Antilipemic	HMG Coa Reductase Inhibitor
f50bn					2													1
f42bf																		
f39mw			2		2								1					
f38bb					2					1							1	1
f38eg		2			2								1			1	1	1
f38ad					2	2									1			1
f36ah					2												1	1
f35kw					2						1						1	1
m34gs	2	2	2	2	2		1											1
m32jf																	1	1
f31ij			2		2						1						1	1
m31tp																		
f31is	2	2	2	2	2						1				1			1
m31ms		2	2		2									1				1
f31mm		2			2										1		1	
f30aw		2			2													1
f29cm					2											1		
f28sg					2		1											1
f28eh		2			2	2												1
m27gm					2												1	
m27ff					2													1
f27lh					2													1
m27rc					2										1			1
m26hb		2			2													1
f26jc	2				2													
m26cq					2													1
f25ml		2			2													1
f25aj																		
f25js					2										1			1
m24wt					2										1			1
m24lh			2		2							1				1		1
f24gs					2												1	1
m24js																1		1
f23hm																		
f23ch					2				1									1
m22pp					2													1
f22vb					2			1										
f22sp					2												1	1
f22pv	2	2	2		2										1			1
m21er					2													1
m20ru		2			2													1
m19pb																		1
m19mg					2											1		1
m18rt					2													1
Count	4	11	7	2	37	2	2	1	1	1	3	1	2	1	7	5	10	34

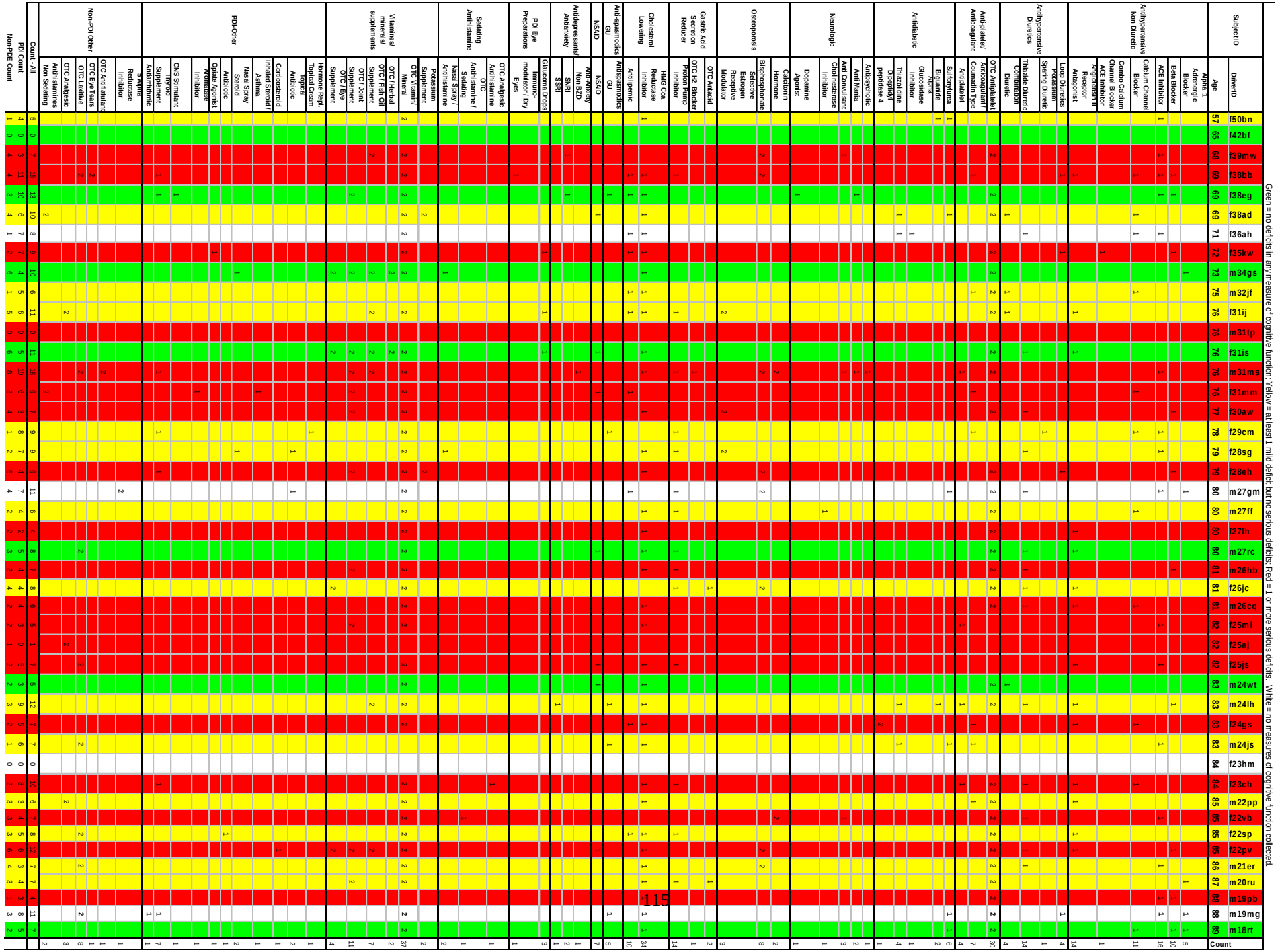
Subject ID	Gastric Acid Secretion Reducer			Osteoporosis			Neurologic					Antidiabetic				
DriverID	Proton Pump Inhibitor	OTC H2 Blocker	OTC Antacid	Selective Estrogen Receptive Modulator	Bisphosphonate	Calcitonin Hormone	Dopamine Agonist	Cholinesterase Inhibitor	Anti Convulsant	Anti Mania	Antipsychotic	Dipeptidyl peptidase 4	Thiazolidine	Alpha Glucosidase Inhibitor	Biguanide	Sulfonylurea
f50bn															1	1
f42bf																
f39mw					2				1							
f38bb	1				2											
f38eg							1			1						
f38ad													1			1
f36ah													1	1		
f35kw																
m34gs																
m32jf																
f31ij	1			2												
m31tp																
f31is																
m31ms	1	1			2	2			1	1	1					
f31mm																
f30aw				2												
f29cm	1															
f28sg	1			2												
f28eh					2											
m27gm	1				2											1
m27ff	1							1								
f27lh																
m27rc	1															
m26hb	1															
f26jc	1		1		2											
m26cq																
f25ml																
f25aj																
f25js	1															
m24wt																
m24lh													1		1	
f24gs												2				
m24js													1			1
f23hm																
f23ch	1															
m22pp																
f22vb						2			1							
f22sp	1															
f22pv					2											
m21er					2											
m20ru	1		1													
m19pb																
m19mg																1
m18rt																1
Count	14	1	2	3	8	2	1	1	3	2	1	1	4	1	2	6

Subject ID	Anti-platelet/ Anticoagulant			Antihypertensive Diuretics				Antihypertensive Non Diuretic					
DriverID	Antiplatelet	Anticoagulant / Coumadin Type	OTC Antiplatelet	Combination Diuretic	Thiazide Diuretic	Potassium Sparing Diuretic	Loop Diuretics	Angiotensin II Receptor Antagonist	ACE Inhibitor Channel Blocker Combo Calcium	Calcium Channel Blocker	ACE Inhibitor	Beta Blocker	Alpha 1 Adrenergic Blocker
f50bn											1		
f42bf													
f39mw			2								1		
f38bb		1					1	1		1	1	1	
f38eg			2								1	1	
f38ad			2	1						1			
f36ah					1					1	1		
f35kw			2				1		1			1	
m34gs			2										1
m32jf		1	2	1						1			
f31ij			2	1				1					
m31tp													
f31is			2		1			1					
m31ms	1		2								1		
f31mm		1								1			
f30aw			2		1							1	
f29cm		1				1				1	1		
f28sg					1						1		
f28eh			2				1					1	
m27gm			2		1						1		1
m27ff			2							1			
f27lh			2					1					
m27rc			2		1			1					
m26hb			2		1							1	
f26jc			2		1			1					
m26cq			2		1			1		1			
f25ml	1										1		
f25aj													
f25js								1			1		
m24wt			2	1									
m24lh	1		2		1			1				1	
f24gs		1						1		1			
m24js		1									1		
f23hm													
f23ch	1		2		1			1		1			
m22pp		1	2					1					
f22vb			2		1						1		
f22sp			2					1					
f22pv			2		1			1				1	
m21er			2		1						1		
m20ru			2										1
m19pb			2								1	1	
m19mg			2				1				1		1
m18rt			2							1		1	1
Count	4	7	30	4	14	1	4	14	1	11	16	10	5

Color Coded According to Unalerted BRT: Red = slowest > 1356; Yellow=>1065 and <=1356; Blue = >877 and <=1065; Green = fastest <=877

MEDICATION USE IN THE 12-HOUR PERIOD PRIOR TO THE OT EVALUATION, BY LEVEL OF COGNITIVE DEFICIT.

Green = no deficits in any measure of cognitive function; Yellow = at least 1 mild deficit but no serious deficits; Red = 1 or more serious deficits. White = no measures of cognitive function collected. 1=PDI Drug Class; 2=Non-PDI Drug Class



Appendix H

Features of Each Database Identified as a Potential Candidate For NHTSA Research Purposes.

Database	N of Database	E –Codes	Pharmacy data	Demographic Data	Special Consideration
Medicaid Analytic eXtract (MAX) Database	~ 7 million individuals age 65+	▪ Present for ~ 25% of claims reporting injury diagnoses, but more likely to be present for higher severity episodes (present in 45-55% of the claims). ▪ Often contain only 3 digits (i.e., 4th digit to identify the injured person as a passenger or the driver is missing).	▪ For outpatient services only. ▪ NDC code; requires a filter to obtain therapeutic drug class. ▪ Prescribed date ▪ Fill date ▪ New or refill ▪ Days supply ▪ Other First Data Bank Proprietary data (Access restricted to license holders): NDC format, drug class, multi source code, HICL, therapeutic class-general, therapeutic class-specific, American hospital formulary code, Smart key, Medispan code, over-the-counter indicator	▪ Date of Birth ▪ Age Group ▪ Sex ▪ Race/Ethnicity ▪ State ▪ County of Residence ▪ Zip Code of Residence	Data Limitations: ▪ Churning eligibility (people are enrolled in Medicaid intermittently). ▪ Minimal info on other insurance coverage. ▪ Income data are unavailable. ▪ Only Medicaid-covered services are present. ▪ Services are incomplete for people with dual eligibility (only the residual after Medicare payment), and for people in pre-paid plans. ▪ CMS does no custom programming or data extraction (i.e., CMS will provide the full file). ▪ Feasibility of database for future NHTSA work very limited.
Medicare Current Beneficiary Survey (MCBS)	Sample size of 12,000 individuals ranging in age from 0 to 85+, with the 85+ sample overrepresented by a factor of 1.5.	▪ Unreliable; only available when required for billing purposes. ▪ Unlikely to have 4th digit	▪ No pharmacy or prescription claims data; only self-reported medication use.	▪ SSN ▪ Age ▪ Gender ▪ Race/Ethnicity ▪ Income ▪ Marital Status ▪ Living Arrangements (lives alone, with spouse, with children, with others). ▪ Schooling ▪ Metropolitan Area resident	▪ Impossible to determine what medications the sample was taking on the date of a claim for hospital services, because there are no pharmacy or prescription claims data; only self-reported medication use. ▪ Database not feasible for future NHTSA research.

Database	N of Database	E –Codes	Pharmacy data	Demographic Data	Special Consideration
Veteran's Health Administration (VHA) Pharmacy Benefits Management (PBM) Database	~ 8 million veterans Nationwide use the VA for healthcare, and 5.1 million of them get their prescriptions from inside of the VA system	▪ Available for approximately 50% of the injury discharges.	▪ Outpatient pharmacy data currently only viable for research ▪ NDC Code ▪ Station product name or description ▪ VA product name ▪ VA drug class ▪ Regional formulary indicator ▪ National formulary indicator ▪ Fill date ▪ Prescription number ▪ Quantity dispensed ▪ Dispensing unit ▪ Dosing instructions ▪ Days supply ▪ New fill/refill/partial indicator ▪ Mail or pickup window indicator ▪ Medication counseling acceptance indicator ▪ Purchase price	▪ SSN ▪ Scrambled SSN ▪ Date of Birth ▪ Age ▪ Gender ▪ Low-income identifier (means test) ▪ Zip Code	▪ Use of data requires a collaborative agreement with a VA investigator. ▪ Cost for data and data cleaning for a study population would average $30,000, not including data analysis services by VA, if needed. Data analysis would increase the cost by $25,000 to $75,000. ▪ Database feasible for future NHTSA research.
General Practice Research Database [United Kingdom]	▪ 3 million current patient records (8.9 million total patient records). ▪ 17% of the sample is patients age 65+	Codes V40.n to V48.n are available to distinguish car-related events; codes identify whether the patient was the driver or a passenger. Percentage of injury discharges with E-codes could be made available at a later date, if required (it is presently unknown).	▪ Drug name ▪ Medical condition for which drug prescribed ▪ Active ingredient ▪ NDC code ▪ Quantity provided ▪ Strength ▪ Decoded therapeutic class ▪ Days supply ▪ Date prescription written	▪ Socioeconomic class ▪ Regional markers (rather than zip code) ▪ Age ▪ Date of birth (year only would be released) ▪ Gender	▪ The cost of a dataset ranges from $14,000 to $120,000. ▪ Database feasible for future NHTSA research, although not an American population.

Database	N of Database	E –Codes	Pharmacy data	Demographic Data	Special Consideration
Nationwide Inpatient Sample (NIS)/Healthcare Cost and Utilization Project (HCUP)	▪ Data from 8 million hospital stays each year, from 1988-2004. ▪ Contains discharge-level records, not patient-level records	▪ E-code completeness on injury records averaged 87% across 33 States. MVCs accounted for 18% of all unintentional injuries	▪ HCUP contains no pharmacy data, nor can it be linked to pharmaceutical data	▪ Age ▪ Gender ▪ Median household income for patient's zip code ▪ Race	▪ Database not feasible for future NHTSA research as it contains no pharmacy data, nor can it be linked to pharmacy data.
Kaiser Permanente	▪ 8.3 million members Nationally ▪ Northern CA region (largest region): 3.3 million members with 600,000 members age 65+	▪ Availability of E-code data unknown	▪ 80 databases can be linked, providing pharmacy data, diagnoses, radiology, clinical laboratory data, and pathology data.	▪ Available but specific variables not identified in this task	▪ Database not feasible for future NHTSA research as Kaiser will not provide data; they only do in-house research on topics of interest to their staff and members. ▪ Also, if etiology data are not coded, chart reviews to pull out MVCs would be cost-prohibitive.
Independence Blue Cross	Not provided	Not provided	Not provided	Not provided	Database not feasible for future NHTSA research for several reasons: ▪ IBX outsources all drug claims for payment ▪ It is unlikely that e-codes are available ▪ Concern in IBX legal dept. regarding patient privacy ▪ No in-house interest at IBX for collaboration on this topic

Database	N of Database	E –Codes	Pharmacy data	Demographic Data	Special Consideration
Ingenix LabRx® (United Healthcare) Database	▪ 35 million patients, 61% of which have at least 1 pharmacy claim, 5.5% of which are age 65+ ▪ Number of older patients should increase in the coming years with acquisition of Pacific Care and Ovations	▪ Available, most often with 4-digit codes than with 3-digit codes. ▪ Percentage of injury claims with E-codes not presently known, however, preliminary data run identified 126 members age 65+ with 4-digit E-codes in the range of E8130 to E8139.	▪ Drug Dispensed (NDC) ▪ Therapeutic Drug Class ▪ Quantity and Date Dispensed ▪ Drug Strength ▪ Days Supply ▪ Dollar Amounts	▪ Gender ▪ Age ▪ Income ▪ Net Worth ▪ Education ▪ Race & Ethnicity ▪ Life Stage ▪ Life Style Indicators	▪ Approximate cost to provide a data file to NHTSA that includes 40,000 patients with 2 years of data, is $50,000. ▪ Database feasible for future NHTSA research.
HMO Research Network **1 of 7 Centers for Education and Research on Therapeutics/CERTS**	Not provided	The center has considered research such as that proposed in the current project, and has concluded that the health plan records included in this Network were probably unable to satisfactorily identify the operators of vehicles involved in motor vehicle crashes. Participation of the Network would require developing a linkage agreement with relevant motor vehicle registries.	Not provided	Not provided	▪ In addition to the limitation of this database resulting from lack of complete E-code data, HMO CERT often collaborates with external investigators but doesn't work as a data vendor. ▪ Database not feasible for future NHTSA research

Appendix I

Questions for Insurance Claims Database Administrators

A research activity under NHTSA Task Order NTS-01-5-05194, Contract DTNH22-02-D-85121
"A Pilot Study to Test Multiple Medication Usage and Driving Functioning"

- Do you have linked medical, hospital, and pharmaceutical data? If yes….
    - How are they linked?
    - Are the ID codes patient-specific (i.e., are family members clearly separated)?
    - Are the claims in one database?
    - What coding systems are used for diagnosis, procedures, and pharmaceutical claims?
    - How many digits are used in the medical claims coding (e.g. 4th digit or 5th digit ICD9-CM)?
    - What is the time lag for the various types of claims?
    - How are claims reversals handled?
    - How is continuity of eligibility tracked?

- Are ICD9-CM "E" codes —codes assigned by trauma registrars and medical record coders in hospitals and doctors' offices to identify the causes of external injury—present in the database to indicate the reason a patient received emergency room or other medical service, and incurred the medical claim?

- What percent of *injury* discharges following inpatient service have an E-code (of any type)? (One study of the VHA system reported that less than 50% of injury discharges were E-coded, and it referenced recently published national studies of civilian injury hospitalizations where E-coding was present for 60% of the discharges).

- What percent of services for treatment of *injuries* during outpatient visits are E-coded?

- Do E-codes that are associated with a motor vehicle crash (motor vehicle traffic accident codes E810 to E819) have the 4th digit to identify the injured person (e.g., 0 for <u>driver</u> of a motor vehicle other than a motorcycle vs. 1 for <u>passenger</u> in a motor vehicle other than a motorcycle)?

- Is there a data checking process to ensure accuracy of E-code assignment and entry into the database for driver vs. passenger? (Because the influence of medication is only relevant to the <u>driver</u> in a crash, and misdesignation of driver vs. non-driver could influence the results of the analyses).

- Is the date of the motor vehicle crash available in the database? If no, can the date of an emergency room visit or hospital or medical service associated with the diagnosis code of motor vehicle crash be obtained?

- Are claims for both inpatient and outpatient visits available in the database?
    - If yes, is there a designation for the place of service?

- How many patients are in the database?

- What percentage of the patients are age 65 or older?

- Is zip code of patient residence available (as a surrogate for urban vs. rural residence) and able to be released (HIPAA)?

- Would patient age and/or date of birth be able to be released (HIPAA)?

    - If not, would patient age be available for release?
    - If age is not available, are strata indicators available for the patients?

- Would patient gender be able to be released (HIPAA)?

- Would it be possible to determine what prescriptions were filled or refilled within a specified window of time (in proximity to the motor vehicle crash occurrence).

- How are the drugs coded (e.g., NDC?). How are the drug classes coded? Is it possible to identify the drug as well as its therapeutic class without using proprietary software?

- Associated with each prescription drug, is the following information available:

    - Medical condition for which the drug was prescribed?
    - Major drug class, drug name, active ingredient, NDC code?
    - Date the prescription was filled?
    - Quantity provided?
    - Strength of medication?
    - Decoded therapeutic class?
    - Days Supply
    - Are claims reversals backed out with the corresponding claim, so as to not have 3 claims for one fill?

- Does the database contain all claim information for a patient, regardless of what physician he/she saw and what pharmacy he/she used to obtain prescriptions (i.e., is the database the central "clearing house" for patients with plan coverage? Is there a way to track prescriptions obtained by mail order or Internet (e.g., drugstore.com)

- Is it possible to determine the duration of treatment for the various drugs prescribed, so that de novo exposure and prolonged exposure vs. crash risk can be assessed? (New users of a drug may initially be at higher risk of a crash, whereas long-time users may have lower risks because they are better acquainted with the adverse effects of the medicine).

- Is there a variable indicating that the patient has other coverage?

- Are data complete for the over-65 patients, that is, if they have crossover claims from Medicare, Medicaid, Veteran's Administration, other commercial insurances are they available in the database?

    - If not, do databases need to be linked somehow, for the data to be all inclusive? If linking is required, is this do-able (by the database administrator, as the data will be anonymized by the time it reaches the researchers)?

- How long are records available for use (in longitudinal studies) before being archived? (NHTSA would need at least 90-180 days before an index event date plus a buffer period. Additional time will be needed to determine "effectively" de novo exposure).

- Are there any known irregularities, inconsistencies, or omissions in the database, with respect to any of the aforementioned variables? If yes, which variables, and what are the coding anomalies?

- What would be the cost of having selected data fields including, but not limited to, those referenced above extracted from the database, anonymized, and delivered to NHTSA?

- What procedures are required to submit a request for data?

- Are there any known barriers to the release of these data to NHTSA?

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**National Highway
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