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THE EFFECT OF VARIABILITY IN SUBSTANCE ABUSE AND DEPENDENCE
TERMINOLOGY ON PHYSICIANS' PRESCRIBING DECISIONS

A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy at Virginia Commonwealth University.

by

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Dedication

*This dissertation is dedicated with all my love to my new baby daughter,
Kayleigh Mae Phipps,
Who reminds me daily what is truly important in life;
To her father, my husband and best friend,
Eric Daniel Phipps;
And to any children who are not quite yet a twinkle in our eyes.*

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“Remember that YOU are the one who has to stand up there and defend it.”

- Dr. Patty Slattum

“Remember that no dissertation project is going to save the world.”

“When the only tool that you have is a hammer, everything starts to look like a nail.”

- Dr. Lilian Hill

“Thou shall not interpret randomness.”

“One of the most important things you learn in graduate school is that there is a lot of stuff you don’t know.”

“Real life is cumulative.”

- Dr. Al Best

“There is a Buddhist belief that my father told me once: If you have a choice to go down two paths but do not know which one to pick, choose the harder one. This is because the harder path will allow for more growth of spirit and person.”

- Dr. Susanna Wu-Pong

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Walt Disney World®: Thank you for existing. Guess what I’m going to do next?

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Abstract

THE EFFECT OF VARIABILITY IN SUBSTANCE ABUSE AND DEPENDENCE TERMINOLOGY ON PHYSICIANS' PRESCRIBING DECISIONS

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Prescription drug abuse is a continuing problem in the United States. Educating physicians on issues related to prescription drug abuse is a key factor in preventing and treating this problem. High variability has been found in substance abuse terminology in the literature, textbooks, and FDA-approved product labeling. This dissertation describes a survey study designed to address how the variability in substance abuse terminology, specifically package inserts, affects the prescribing decisions made by physicians.

A random sample of 1008 physicians currently licensed and residing in the Commonwealth of Virginia received a letter of explanation, a self-administered questionnaire, and a follow-up reminder and thank you. To increase response rate, a second questionnaire was sent to non-responders. Prescribing decisions made by physicians were measured as three variables: comfort level with a prior physician's choice, likelihood of refilling the prescription, and likelihood of prescribing a drug or drug class as the first physician seeing a particular patient. Physicians were presented with four case scenarios which included package insert information and selected patient characteristics. Other factors affecting physicians' decisions in prescribing controlled substances include ideas about addiction, and characteristics of the physician, patient, disease state, and drug. The patient case scenarios and other items on the questionnaire addressed these covariates.

Based on the number of deliverable questionnaires returned and included in analysis, the response rate was 32.3%. More physicians associated abuse, craving, drug-seeking behavior, psychological dependence, and withdrawal with addiction than with drug dependence, while more physicians felt that physical dependence and tolerance were necessary for drug dependence. The most frequently used sources for drug information were the Physicians' Desk Reference (PDR), package inserts, and pharmacists.

Four linear regression models were created for physician prescribing decisions. Physician, patient and package insert characteristics were all significant ($p < 0.05$). Interaction terms for type of pain and history of substance abuse were also significant, indicating that the importance of substance abuse history is dependent on the type of pain being treated.

CHAPTER 1

Introduction

Overview of the Document

This dissertation describes a survey research study designed to investigate how the variability in substance abuse and dependence terminology in package inserts affects prescribing decisions made by physicians, explore how physicians define “drug dependence” and “drug addiction,” and identify the sources used by physicians for drug information. This chapter provides background information on prescription drug abuse in the United States, the history of substance abuse and dependence terminology, and factors affecting physician prescribing decisions. Chapter 2 presents a more in depth overview of the literature of terminology, package inserts, and physician surveys. Chapter 3 provides details on a preliminary study of package insert information specifically on substance abuse and dependence information. Chapter 4 describes the methodology used for this survey study, Chapter 5 portrays its results, and Chapter 6 summarizes and discusses conclusions from the study.

Prescription Drug Abuse in the United States

Dr. Alan Leshner, the Director at the National Institute on Drug Abuse (NIDA), stated in a July 2001 research report that “abuse of prescription drugs remains a serious public health concern.” (National Institute of Drug Abuse (NIDA), 2001).

Looking specifically at non-medical use of prescription drugs, four categories are examined by the National Survey on Drug Use and Health (NSDUH). They are: pain relievers, stimulants, tranquilizers, and sedatives. Non-medical use is classified as intake of a prescription medication that is not prescribed for the person using it or use only for the feeling that is caused by the drug. Table 1.1 shows, for 1990 and 2001, the number of people using these four categories of prescription drugs for non-medical use.

Table 1.1 New non-medical users of prescription drugs

Category	1990	2001
Pain relievers	628,000	2,400,000
Stimulants	270,000	808,000
Tranquilizers	373,000	1,100,000
Sedatives	<300,000	<300,000

There is a notable increase in initiation of use of prescription pain relievers, stimulants, and tranquilizers over the 11 years spanning 1990 and 2001. The number of sedative initiates, however, has remained under 300,000 since 1981. Peak use of sedatives was at 638,000 new users in 1977, then steadily dropped off and remained fairly stable, with a slow but steady rise from 111,000 in 1995 to 175,000 in 2000 (OAS, 2003). Clearly, while sedatives have not proven to be as popular for new users, tranquilizers, stimulants, and prescription pain relievers have shown large increases in the estimated number of new users over the 11 years spanning 1990 to 2001.

From 2002 to 2004, first time non-medical use of pain relievers remained steady at about 2.4 million, tranquilizers at about 1.2 million, stimulants remained in the

700,000's, and sedatives continue to remain under 300,000. Data collected before 2002 cannot be compared to data collected after 2002 because of methodology changes, making trend analysis for recent years unreliable. Several more years of data are needed to determine whether any trend is present.

Overall, lifetime non-medical use of psychotherapeutics increased significantly from 32.4 million to 36.0 million from 2000 to 2001 ($p<0.01$) (OAS, 2001). The increase in past-year prevalence, from 3.9% (8.76 million) to 4.9% (11.10 million), and the increase in past-month prevalence, from 1.7% (3.85 million) to 2.1% (4.81 million) was also significant ($p<0.01$) (OAS 2001). From 2002 to 2004, lifetime non-medical use of psychotherapeutics increased from 46.8 million to 48.0 million, and lifetime non-medical use of pain relievers increased from 29.6 to 31.8 million users ($p<0.05$) (OAS, 2004). Past-year prevalence has remained steady at about 14.6 million users, or about 6.2% of the population (OAS, 2004). Past-month prevalence, a measure of current use, has also remained steady, at about 6 million or 2.5% of the population (OAS, 2004).

Some may argue that drugs like heroin pose a much larger problem than abuse of prescription drugs. On January 21, 2005, the Substance Abuse and Mental Health Services Administration (SAMHSA) released a new report based on data collected from the NSDUH in 2002 and 2003. This report was comparing non-medical use of oxycodone to heroin use. From 2002 to 2003, the prevalence of lifetime non-medical use of oxycodone increased from 11.8 million to 13.7 million users, from 5.0 to 5.8%. Heroin use, however, remained steady at 1.6% prevalence of lifetime use (OAS 2005). This suggests that people may be turning to prescription drugs as an alternative to illicit

drug use, although further data are needed to determine whether or not this is an incidental phenomenon or a trend over time. Further evidence supporting this theory was reported in a recent publication from NIDA, stating that while the abuse of some drugs such as LSD (lysergic acid diethylamide) and Ecstasy fell, the lifetime abuse of prescription medications, particularly narcotic painkillers, has significantly increased from 2002 to 2003. The young adult age group (18-25 years) showed a 15% increase in lifetime and past-month non-medical use of pain relievers (OAS, 2004).

Whether or not the increasing trends in the prevalence and incidence of new use of prescription drugs for non-medical use reflects abuse of drugs depends on how “abuse” is defined. If any use of a substance specifically for the feeling it causes and not for a prescribed indication is considered abuse, then the above statistics suggest an increase in abuse. If a diagnosis of a substance abuse or dependence disorder is required, a different set of reports must be examined.

The July 2004 Drug and Alcohol Services Information System (DASIS) report points out that between the years of 1992 and 2002, the rate of admission for treatment for the abuse of narcotic painkillers more than doubled (OAS 2004). The total number of treatment admissions between 1997 and 2002 increased by 17%; however, the number of admissions for primary abuse of narcotic painkillers rose 186%, while treatment admissions for heroin abuse increased by 21% (OAS 2004). This is strongly indicative of an increase in prescription drug abuse, specifically that of narcotic painkillers.

Both the non-medical use of prescription drugs and treatment admission rates for prescription drug abuse have been on the rise, particularly in the last 5–10 years. These

trends unmistakably convey that prescription drug abuse in the United States is a public health problem.

Terminology of Substance Abuse and Dependence

The definitions of addiction, abuse, and dependence have been debated by scientists and researchers for decades. Numerous review and opinion papers propose definitions and appropriate use of the words. In 2001, the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine formed the Liaison Committee on Pain and Addiction (LCPA), and developed working definitions of “addiction, physical dependence, and tolerance” and recommended their use (Savage, Joranson, Covington, Schnoll, Heit, Gilson 2003). Addiction was defined as “a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.” (Savage et al 2003). Physical dependence was defined as “a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.”(Savage et al 2003). Tolerance was defined as “a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.” (Savage et al 2003). The LCPA has not yet provided

definitions for “psychic or psychological dependence,” and “abuse,” two other terms of interest in this study.

Two NIDA websites refer to the Diagnostic and Statistical Manual of Mental Disorders, 3rd and 4th editions (DSM-III-R and DSM-IV) for criteria-based definitions of substance abuse and dependence and offer working definitions of “psychoactive substance use,” “psychoactive substance abuse (or problematic use),” and “addiction.” (available at <http://165.112.78.61/Diagnosis-Treatment/Diagnosis2.html>, <http://www.nida.nih.gov/Drugpages/DSR.html>). One website indicates that “drugs may be used in a socially accepted or medically sanctioned manner to modify mood or state of mind.” Having a drink with a friend or taking anxiolytic agents for anxiety as directed by a physician is classified as psychoactive substance use. “Psychoactive substance abuse or problematic use” is defined as “the use of a substance...in a manner that is illegal or harmful to oneself.” A distinct definition of “addiction” is not given, although the website describes it as being “characterized by the repeated, compulsive seeking or use of a substance despite adverse social, psychologic and/or physical consequences” (available at <http://www.nida.nih.gov/Drugpages/DSR.html>).

Ferrell and colleagues performed a qualitative assessment of information in fourteen textbooks about opioid use and addiction potential. They found that information, based on the researchers’ definition of “addiction,” was more often inaccurate than not, and highly varied in how “addiction” was defined and used (Ferrell, McCaffery, and Rhiner, 1992).

In a survey of 500 physicians, researchers gathered data about general knowledge of practitioners in the area of pain management, including the definition of “addiction” and legal issues associated with prescribing controlled substances. Addiction was defined in a variety of ways by survey respondents, even when it was presented as a multiple choice question (Greenwald, Narcessian, and Pomeranz, 1999).

The Federal Controlled Substances Act of 1970 also uses the word “addiction,” stating that an addict is one “who is so far addicted to the use of narcotic drugs as to have lost power of self-control with reference to his addiction” (available at <http://www.usdoj.gov/dea/agency/csa.htm>). The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) does not use the word “addiction,” but instead gives criteria for “substance abuse” and “substance dependence,” respectively (American Psychiatric Association (APA), 2000). Clearly, there is a lack of consensus of the definition and use of the language of substance abuse and dependence.

Factors Affecting Physicians’ Prescribing Decisions

A survey study by Potter et al in 2001 determined that a low level of concern about physical dependence, tolerance, and addiction was the most significant predictor of the willingness of a physician to prescribe opioids to patients with chronic non-malignant pain. The year of graduation from medical school was found to be significant in two models at p-values of 0.0025 and 0.0048 (Potter, Schafer, Gonzalez-Mendez, Gjeltema, Lopez, Wu et al., 2001). Specifically, more recent graduation from medical school increased willingness to prescribe under the conditions of the models. Additionally,

concern about regulatory scrutiny was significant ($p=0.0424$), with fear of regulatory scrutiny limiting the willingness to prescribe opioids (Potter et al., 2001).

In a 1994 study of physicians conducted by Turk and colleagues, 1912 of 6962 physicians (response rate 27.46%) returned a questionnaire with items regarding years of practice, frequency of long-term treatment with opioids, number of chronic pain patients treated, and concerns about regulatory pressure, among other variables. The purpose of this study was to assess the attitudes and practices of physicians with regard to long-term prescribing of opioids for non-cancer pain. There was a significant difference found in the frequency of prescribing opioids long-term among the specialties (ANOVA $p<0.001$). Rheumatologists were significantly more likely to prescribe opioids long-term than any other specialty ($p<0.003$) (Turk, Brody, Okifuji, 1994). This suggests that specialty is a predictor of physician prescribing decisions but provides no information on the significance or amount of the variance explained in physician prescribing decisions.

Weinstein and colleagues from the University of Texas also conducted a survey about the use of opioid analgesics. A 59-item questionnaire was employed to identify how physicians' attitudes and knowledge contribute to pain management practices. Four scales were identified: reluctance to prescribe opioids, fear of patient addiction, tolerance, or dependence, fear of regulatory agency scrutiny, and knowledge about pain and its treatment. Correlating the fear of regulatory scrutiny scale with medical discipline revealed that internists had decreased fear compared to anesthesiologists/surgeons, but this difference was not statistically significant (Weinstein, Laux, Thornby, Lorimor, Hill, Thorpe, and Merrill, 2000).

Another survey examining prescription decisions used a series of 24 patient cases to measure physician prescribing of benzodiazepines while varying four factors. These four factors were health status, psychiatric diagnosis, stability of job and marriage, and short-term ability to work. Psychiatric diagnosis and the health status of an alcohol-related medical problem were found to be significant predictors of agreement to prescribe benzodiazepines. Added to the regression model were physician characteristics of year of graduation from medical school and specialty, among others. This study did not find the physician characteristics to be significant with regard to physician prescribing decisions (Brown, Brown, Saunders, Castelaz, and Pappasoulitis, 1997).

A survey of emergency department physicians also used vignettes to identify factors influencing prescribing decisions. One of the specific aims of this project was to “determine whether physicians’ characteristics are associated with either their baseline likelihood of opioid prescribing or their responses to additional information.” Year of graduation from medical school and specialty were among the variables included in physician characteristics examined. This study did not find any significance in any physician characteristics with regard to prescribing of opioid medications (Tamayo-Sarver, Dawson, Hines, Cydulka, Wigdon, Albert, Ibrahim, Baker, 2004).

In summary, factors found to influence physician prescribing decisions include concern about dependence, length of physician practice, diagnosis, fear of regulatory scrutiny, and physician specialty. Other factors found to affect physician prescribing decisions include: potency of drug prescribed, indication for which drug is prescribed, patient's history of drug abuse, familiarity with guidelines, medical discipline

or specialty, and age of physician (Schumock, Walton, Park, Nutescu, Blackburn, Finley, and Lewis, 2004; Davies and Huxley, 1997).

Problem Statement

The review of the literature surrounding substance abuse and dependence terminology prompted a preliminary exploration of package inserts, an important source of information for prescribers. The use of terminology and amount of information in the sample of package inserts studied was found to be highly varied, with no predictable patterns across classes or controlled substance schedules (Phipps, Balster, Slattum, and Kirkwood, in press). Education of health care providers using materials with non-standardized terminology and varied information about substance abuse and addiction could lead to variability in physician understanding. This could affect decisions that physicians make about prescribing medications, which could affect the quality of substance abuse treatment and social aspects of substance abuse research.

Significance

This study aims to increase knowledge about how physicians interpret terminology associated with substance abuse and dependence information in package inserts and to characterize how this variability affects prescribing decisions made by physicians. The information generated in this study can be used as groundwork for additional studies in the communication of information to physicians and the development and evaluation of clearer, more useful package inserts.

Objectives

Prescription drug abuse is an on-going problem in the United States. Educating health care providers about substance abuse issues is an important factor in both the prevention and treatment of prescription drug abuse. Package inserts are an important source of drug information for health care providers, and variability in substance abuse-related terminology use in package inserts is high (Phipps et al, in press). Using survey research methods, this project aims to:

- 1) Describe how physicians define the terms drug dependence and addiction
- 2) Characterize sources used by physicians for drug abuse and dependence and other drug information
- 3) Portray the scope of the problem of varied terminology in package inserts by characterizing its effects on physician prescribing decisions when modeled with covariates of physician and patient characteristics
- 4) Provide groundwork for research designed to evaluate and develop more useful package inserts.

Summary

Review of literature has revealed a lack of consensus of the language surrounding the public health problem of substance abuse and dependence. This project is intended to elucidate how this variability affects prescribing decisions made by physicians.

CHAPTER 2

Literature Review

Overview

This chapter offers a more in-depth review of the literature summarized in Chapter 1 and provides support for the variables included in the survey study.

Prescription Drug Abuse in the United States

The National Survey on Drug Use and Health (NSDUH), formerly known as the National Household Survey on Drug Abuse (NHSDA), is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA). SAMHSA is an agency under the United States Department of Health and Human Services (DHHS). Periodically, SMHSA's Office of Applied Studies (OAS) publishes its findings in a series of reports. These reports provide information about the prevalence and incidence of drug use in the United States.

As stated in the Introduction, NSDUH reports have shown an increase in both incidence and prevalence of non-medical use of prescription drugs over the 11 years spanning 1990 and 2001. The four classes of prescription drugs included in the NSDUH are pain relievers, stimulants, tranquilizers, and sedatives. Non-medical use is defined as “use of prescription-type drugs not prescribed for the respondent by a physician or used only for the experience of feeling they caused.”

A sample of households in the U.S. is randomly selected, and each is personally visited by an interviewer, who obtains consent and administers the questionnaire. Most of the questionnaire is self-administered on a computer, with a few questions asked and entered by the interviewer.

It is important to note that several changes in methodology and analysis occurred in 2002, making it difficult to compare data collected before 2002 to data collected from 2002 onward. One of the changes in methodology that occurred in 2002 is the name change of the survey from National Household Survey on Drug Abuse to the National Survey on Drug Use and Health. Because of the problem of social desirability in survey research, the current name could have had an impact on response rate, particularly those who do not use drugs recreationally, as they may be less likely to participate in a survey on “drug abuse” than on “drug use and health.” A second change in methodology is the addition of a \$30 incentive for participants, which could also affect response rate in the general population. In fact, the response rate increased from ~73% in 2000 to ~78% in 2002, and has remained at about 78% for 2003 and 2004 (NHSDA 2000 and NSDUH 2004). Other changes have included techniques employed for weighting the samples, wording and addition of questions, and format of the informational brochure given to respondents.

Chapter 1 of this document illustrated the escalation in incidence of prescription drug categories from 1990 to 2001. New non-medical use of pain relievers proved the largest increase, from 628,000 in 1990 to 2.4 million in 2001 (Office of Applied Studies (OAS), 2003). For the same years, new users of stimulants rose from 270,000 to 808,000

and tranquilizer initiation soared from 373,000 to 1.1 million. New use of sedatives, however, has remained under 300,000 new users since 1981. Initiation of sedatives peaked at 638,000 in 1977, then steadily dropped off and remained fairly stable. While the number of new users of sedatives has remained under 300,000, it has recently begun a slow but steady rise, from 111,000 in 1995 to 175,000 in 2000 (OAS, 2003). Clearly, while sedatives have not proven to be as popular for new users, tranquilizers, stimulants, and especially prescription pain relievers have shown large increases in the estimated incidence of new use over the 11 years spanning 1990 to 2001. It is interesting to note that there seems to be an actual decrease in new use of these three categories of drugs from 2000 to 2001. Pain reliever initiation dropped from 2.7 to 2.4 million, tranquilizers from 1.3 to 1.1million, and stimulants from 983,000 to 808,000 (Office of Applied Studies, 2003). Because of the aforementioned methodology changes of 2002, however, data collected beyond this point cannot be used to determine whether or not this is the beginning of a downward trend.

In recent years, new use of prescription drugs for non-medical purposes seems to have stabilized. From 2002 to 2004, first time non-medical use of pain relievers lingered at ~2.4 million, tranquilizers at ~1.2 million, stimulants steadied in the 700,000's, and sedatives continue to remain under 300,000. (<https://nsduhweb.rti.org/>). As stated previously, however, because of the methodology changes of 2002, data collected before 2002 cannot be compared to data collected after 2002, making trend analysis for recent years unreliable. Several more years of data are needed to determine whether any trend is present, with 2002 data serving as a new baseline.

In addition to incidence, or new use of prescription drugs, SAMHSA gathers information on lifetime prevalence and estimates past-year and past-month prevalence. From 2000 to 2001, lifetime non-medical use of prescription drugs significantly rose from 32.4 million to 36.0 million ($p < 0.01$) (OAS, 2001). Also significant at the $p < 0.01$ level are the increases in past-year prevalence, from 3.9% (8.76 million) to 4.9% (11.10 million), and past-month prevalence, from 1.7% (3.85 million) to 2.1% (4.81 million) (OAS 2001). Past-month prevalence is indicative of current use.

From 2002 to 2004, overall lifetime non-medical use of psychotherapeutics has increased from 46.8 million to 48.0 million (<http://oas.samhsa.gov/nhsda.htm>). Again, it is important to mention that a conclusion cannot be drawn about the apparent increase from 36.0 million in 2001 to 46.8 million in 2002. Past-year prevalence has remained steady at about 14.6 million users, or about 6.2% of the population, as has past-month prevalence, at about 6 million or 2.5% of the population (<http://oas.samhsa.gov/nhsda.htm>).

In 2002, the prevalence of non-medical pain reliever use in the U.S. was estimated at 13%, or almost 30 million people aged 12 or older (Office of Applied Studies, 2004). Males were more likely than females to have used a prescription pain reliever non-medically (14.3 vs. 11.0%) in their lifetime, and Caucasians were more likely than other race/ethnicities (White: 13.6%, Black: 9.7%, Asian: 7.0%, Hispanic: 11.0%).

It is interesting to note that with regard to specific substances, tramadol, a non-controlled pain reliever available only by prescription, was used nonmedically by approximately 1 million people, which is similar to the estimated use of methadone (0.9

million) and Dilaudid® (1.1 million) (Office of Applied Studies, 2004). OxyContin® and morphine users were at 1.9 and 2.1 million, respectively. The most highly used pain relievers were found to be propoxyphene containing (Darvocet® and Darvon®), and Tylenol® with codeine, at 18.9 million, followed by hydrocodone products (Vicodin®, Lortab®, and Lorcet®) at 13.1 million (OAS, 2004). Codeine products weighed in at 6.9 million users.

Looking at the data collected from 2002 to 2004, lifetime non-medical use of pain relievers has increased from 29.6 to 31.8 million users ($p < 0.05$). Again, propoxyphene containing products remained the most commonly used pain relievers at 9.0%, followed by hydrocodone and then oxycodone containing products at 7.9% and 4.9%, respectively. Tramadol containing products were estimated as being used by 0.5% of the population (<http://oas.samhsa.gov/nhsda.htm>).

While in the youth age group (12 – 17 years), lifetime non-medical pain reliever use prevalence seems to have risen from 2001 to 2002 (9.6 to 11.2%) and non-medical stimulant use prevalence from 3.8 to 4.3%, it is difficult to interpret this phenomenon because of the previously mentioned changes in measurement methodology from 2001 to 2002. In recent years, however, the overall prevalence of lifetime non-medical use of pain relievers in youths aged 12-17 years has remained fairly constant, at 11.2% in 2002 and 11.4% in 2004. However, the non-medical use of Oxycontin® has increased in prevalence from 0.9 to 1.2% ($p < 0.05$). Lifetime use of stimulants has decreased in prevalence from 4.3% to 3.4% ($p < 0.01$), and prevalence for tranquilizers and sedatives

has remained constant at about 3.3% and 1.0%, respectively (<http://oas.samhsa.gov/nhsda.htm>).

Some may argue that illicit drugs like heroin pose a much larger problem than abuse of prescription drugs. On January 21, 2005, SAMHSA released a new report based on data collected from the NSDUH in 2002 and 2003. This report was comparing non-medical use of oxycodone to heroin use. From 2002 to 2003, the prevalence of lifetime non-medical use of oxycodone increased from 11.8 million to 13.7 million users, from 5.0 to 5.8%. Heroin use, however, remained steady at 1.6% prevalence of lifetime use (OAS 2005). Therefore, not only is the prevalence for oxycodone higher than that of heroin to begin with, it is also increasing. This might suggest that people are turning to prescription drugs as an alternative to illicit drug use, although further data are needed to determine whether or not this is an incidental phenomenon or a trend over time. Further evidence supporting this theory was reported in a recent publication from NIDA, noting from the NSDUH 2003 survey that while the abuse of some drugs such as LSD and Ecstasy fell, the lifetime abuse of prescription medications, particularly narcotic painkillers, significantly increased from 2002 to 2003, with the young adult age group (18-25 years) showing a 15% increase in lifetime and past-month nonmedical use of pain relievers (NIDA 2004, OAS 2004).

The Drug and Alcohol Services Information System (DASIS) report is a source of information on substance abuse treatment services. Like the NSDUH report, it is published periodically by the Office of Applied Studies at SAMHSA. As mentioned in the introductory chapter, the July 23, 2004 report indicates that between the years of 1992

and 2002, the rate of admission for treatment for the abuse of narcotic painkillers has more than doubled (OAS 2004). The total number of treatment admissions between 1997 and 2002 increased by 17%; however, the number of admissions for primary abuse of narcotic painkillers rose 186%, while treatment admissions for heroin abuse increased by 21% (OAS 2004). This further underscores the problem associated with abuse of prescription drugs, particularly pain medications.

This report also reports admission rates by state, as number of admissions per 100,000, in categories of <14, 14-18, 19-23, or ≥ 24 . There is a trend upward in the number of states that have reached the category of $\geq 24/100,000$. Specifically, the number of states reporting admission rates of $\geq 24/100,000$ has increased from 5 in 1992, to 11 in 1997, to 31 states in 2002 (OAS 2004). Notably, the highest rates were in Maine and Connecticut (207 and 89 per 100,000, respectively). This perhaps suggests a need for a shift in the scale of how admission numbers are categorized. A promising trend noted is that the median duration of use before first seeking treatment has decreased. In 1992, people abused drugs for a median of 9 years before first seeking treatment, and this has decreased to 7 years in 1997, and further decreased to 4 years in 2002 (OAS 2004). While this indicates that people are getting treatment faster, this may also mean an increase in the need for resources for treating substance abusers of prescription drugs.

Both the non-medical use of prescription drugs and treatment admission rates for prescription drug abuse have been on the rise, particularly in the last 5–10 years. These trends clearly demonstrate that prescription drug abuse in the United States is a public health problem.

Terminology Variability

As mentioned in the introductory chapter, there are currently many different views on the definition of “addiction.” Numerous committees and organizations have proposed appropriate definitions and use for the term. Some of these have included: the American Psychiatric Association, the National Institute on Drug Abuse, and the Liaison Committee on Pain and Addiction (LCPA) formed by the American Academy of Pain Medicine.

LCPA defined addiction as “a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.”

Two NIDA websites refer to the Diagnostic and Statistical Manual of Mental Disorders, 3rd and 4th editions (DSM-III-R and DSM-IV) for criteria-based definitions of substance abuse and dependence and offer working definitions of “psychoactive substance use,” “psychoactive substance abuse (or problematic use),” and “addiction” (<http://165.112.78.61/Diagnosis-Treatment/Diagnosis2.html>, <http://www.nida.nih.gov/Drugpages/DSR.html>). One website indicates that “drugs may be used in a socially accepted or medically sanctioned manner to modify mood or state of mind.” This is classified as psychoactive substance use, and gives the examples of having a drink with a friend and taking anxiolytic agents for anxiety as directed by a physician. “Psychoactive substance abuse or problematic use” is defined as “the use of a

substance...in a manner that is illegal or harmful to oneself.” A distinct definition “addiction” is not given, although the website describes it as being “characterized by the repeated, compulsive seeking or use of a substance despite adverse social, psychologic and/or physical consequences” (<http://www.nida.nih.gov/Drugpages/DSR.html>).

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) does not use the word “addiction,” but instead gives criteria for “substance abuse” and “substance dependence,” respectively (American Psychiatric Association, 2000).

While no studies specifically addressing substance abuse terminology in package inserts were found, textbook content has been previously examined. A qualitative assessment of information about opioid use and addiction potential in fourteen textbooks was performed by Ferrell, McCaffery, and Rhiner (1992). Of the fourteen texts examined, eight were pharmacology and six were medical/surgical textbooks.

Information was assessed based on two questions:

- 1) Is addiction defined as psychological dependence and distinguished from tolerance and physical dependence in accordance with current definitions used by the American Pain Society (APS) and the World Health Organization (WHO)?
- 2) Is the incidence of addiction accurately stated?

The researchers do not specifically state a definition of addiction that was used as criteria, but in the introduction, they state that addiction is “a psychological and behavioral syndrome characterized by overwhelming involvement with obtaining and using the drug for effects other than pain relief” (Ferrell, et al, 1992). They assert that

only one of the fourteen textbooks used the correct definition of addiction, and that frequently, textbooks used the term “dependence” without specifying physical or psychological. A few of the statements found in the textbooks evaluated are as follows (Ferrell, et al, 1992):

- “Addiction and psychological dependence are defined as separate entities.”
- “Addiction is a process of physiological dependence which is characterized by the two primary components of tolerance and withdrawal syndrome.”
- “All narcotics created psychologic and physical dependence and tolerance...”

A textbook outlining symptoms of morphine abuse included constipation and withdrawal symptoms on the list. The same textbook that was deemed to have the correct definition of addiction was also the only one to also correctly state that the incidence of iatrogenic addiction to opioids when used for medical reasons is less than 1% (Ferrell, et al, 1992). While this study is highly subjective and detailed information about how the qualitative evaluation took place, the results of this study suggest that there is variability in the information used in the didactic training of students entering the health care profession. It did not address drug information resources used by current practitioners.

It stands to reason, then that health care professionals exposed to the variety of sources available to them might differ in how they perceive the term “addiction.” Greenwald et al conducted a survey of 500 psychiatrists in the United States, randomly selected from the list of members of the American Academy of Physical Medicine and Rehabilitation (AAPMR). Each of the selected physicians received a cover letter, a questionnaire, and stamped return envelope. Non-responders received a second packet

three weeks later. A response rate of 50.6% complete enough for analysis was achieved (Greenwald, Narcessian, Pomeranz, 1999). Questionnaire items addressed the types of patients treated, drugs the physicians were willing to prescribe for cancer and non-cancer pain, pharmacologic and legal aspects of opioid use, and the definition of “addiction.” Demographic information gathered included the physicians’ age, state, and the year of medical school completion.

The definition of “addiction” was asked as a multiple choice question. Physicians were asked to choose one or more of the following: physical dependence, tolerance, and/or psychological dependence. An answer of “don’t know” was also an option. Table 2.1 shows the respondents’ answers.

Table 2.1 Definitions of addiction*

Terms chosen	% respondents
Physical dependence, tolerance, and psychological dependence	27
Physical dependence and tolerance	2
Psychological dependence and tolerance	2
Physical and psychological dependence	26
Physical dependence	14
Psychological dependence	25
Don’t know	3

*Data compiled from Greenwald et al 1999

This finding supports the idea that physicians have varying views on what addiction means.

A true/false item on the questionnaire revealed that 14.4% of respondents either thought that a patient would become addicted to opioids if used daily for one month

regardless of diagnosis (8.1%), or did not know (6.3%). This could reflect a misconception of the incidence of iatrogenic addiction to opioids used for legitimate medical purposes; however, it could also be that the respondents differed in their perceptions of “addiction.” Based on the results shown in Table 2.1, only 25% of respondents defined “addiction” as “psychological dependence,” which is what the researchers considered a correct answer (Greenwald et al, 1999).

The sampling frame chosen in this study limits the generalizability of results to members of the AAPMR, and only about 50% of psychiatrists in the U.S. are members (Greenwald et al, 1999). It is possible that psychiatrists in the U.S. who are not members of AAPMR would answer differently from the respondents. Even within the AAPMR sample, there was a difference noted in that 8.4% of respondents belonged to the AAPMR Pain Special Interest Group, but only 4.3% of AAPMR members overall belong to this group (Greenwald et al, 1999). Additionally, because this study focused on specialists in physical medicine and rehabilitation, no conclusions can be drawn about possible opinions of physicians in other specialties.

Factors Affecting Physicians’ Prescribing Decisions

Many studies have aimed at identifying factors that affect decisions that physicians make when prescribing medications. Several of them will be discussed in this section.

In a 1994 study of physicians conducted by Turk, Brody, and Okifuji, 1,912 of 6,962 physicians (response rate 27.46%) returned a questionnaire with items regarding

years of practice, frequency of long-term treatment with opioids, number of chronic pain patients treated, and concerns about regulatory pressure, among other variables (Turk, et al 1994). The stated purpose of this study was to assess the attitudes and practices of physicians with regard to long-term prescribing of opioids for non-cancer pain (Turk, et al 1994). Upon further examination of the methods and analysis, it appears that there was a particular interest in physician specialty and region of practice in the United States. Each of the aforementioned variables was analyzed by ANOVA against physician specialty and region of practice. There were 5 regions of practice: Northeast, Midwest, Southeast, Southwest, and Pacific. Four specialty areas were identified from seven originally chosen. Those four were: general practice, surgery, rheumatology, and neurology/psychiatry. General practice was made up of family practice and internal medicine specialties, while surgery contained neurosurgeons and orthopedic surgeons. Additionally, neurologists and psychiatrists were combined into a single group, called NPM. The sample was a stratified, random sample of physicians in the United States. A random sample of physicians from two states in each of the five regions was chosen to receive a questionnaire.

Frequency of prescribing opioids was measured on a 7-point Likert scale where 0 indicated “never” and 6 was defined as “very frequently.” There was a significant difference found in the frequency of prescribing opioids long-term among the specialties (ANOVA $p < 0.001$) (Turk, et al, 1994). Not surprisingly, rheumatologists were found to prescribe long-term opioids more frequently than any other specialty (mean=1.98, SD=1.45), with surgeons reporting the least frequent prescribing of opioids for persistent

pain (mean=1.14, SD=1.31) (Turk, et al, 1994). The use of parametric statistics for this analysis is questionable. While the sample size was very large and a 7-point Likert scale is often treated as continuous data, the results for the surgery group, specifically a standard deviation greater than the mean, imply that a negative answer was possible, which it was not. Therefore, these results must be interpreted with some caution. It is unknown whether or not Kruskal-Wallis, the non-parametric analogue to ANOVA, would have shown statistical significance. It is also interesting to note the wording of this item on the questionnaire: “How frequently do you prescribe chronic (maintenance) opioids for persistent pain?” While the other items on the questionnaire specify and even stress non-cancer pain in italics, this item indicates only “persistent” pain and could have been interpreted differently by some physicians.

Other items on the questionnaire addressed concerns about addiction, tolerance, and physical dependence. Because these items were found to be significantly correlated ($p<0.001$), they were collapsed into a category designated as “concerns about ATD” (Turk, et al, 1994). The mean score for the items was used as the ATD score. ANOVA indicated that there was a significant difference in these scores among the specialties ($p<0.001$) (Turk, et al, 1994). Again, the greatest difference was between rheumatologists and surgeons, showing the least concern and the greatest concern, respectively, although Tukey’s HSD test indicated that each group differed significantly from the others (Turk, et al, 1994).

With respect to region of the country, frequency of prescribing differed significantly ($p<0.001$), but concerns about ATD did not (Turk, et al, 1994). Physicians

in the Midwest were less likely to prescribe maintenance opioids for persistent pain than those in the Southeast or the West (Turk, et al, 1994). Additionally, physicians in states where multiple prescriptions are required for CII medications demonstrated a significantly lower frequency of prescribing than those states not requiring multiple prescriptions ($p < 0.001$) (Turk, et al, 1994). However, these data must also be interpreted with caution, as there were only three out of the ten states chosen that required multiple prescriptions, indicating the likelihood that the sample sizes were not equal in the groups, as is assumed in ANOVA. Furthermore, the degrees of freedom for the ANOVA were reported as 1 and 1,225 (Turk, et al, 1994). With a returned sample size of 1,912, this is indicative of a large amount of missing data for this question.

The results of this study suggest that practice specialty is a predictor of physician prescribing decisions but provides no information on the significance or amount of the variance explained in physician prescribing decisions.

In 2001, Potter and colleagues conducted a survey of primary care physicians who were part of the University of California, San Francisco/Stanford Collaborative Research Network (CRN). Any member of the network who was not involved with the study was chosen to receive a questionnaire, resulting in a sample size of 230 (Potter et al, 2001). Multiple contacts, including 2 mailed reminders and up to 3 phone calls, were used to increase response rate. The questionnaire was made up of 3 patient case scenarios with follow-up questions, items related to attitudes about opioids and prescribing decisions, and demographics. The purpose of the study was to gain insight into physicians'

attitudes toward the use of opioids in chronic, non-malignant pain (CNMP) and factors affecting willingness to prescribe opioids.

The dependent variable, willingness to prescribe opioids, was measured in three ways. First, a sum scale was created from answers to the follow-up question from the vignettes: “If the pain persisted unchanged, would you prescribe opioids for this patient on a long-term basis?” The second model was measured as level of agreement with a statement about prescribing CIII medications on an as-needed basis for CNMP, and the third model for CII medications on a scheduled basis for CNMP.

Independent variables included patient variables, which were included in the vignettes, and physician demographics. There were 2 significant predictors for the first model and three each for the second and third models. Lower level of concern about physical dependence was a significant predictor of willingness to prescribe opioids in all three models, with R^2 values of 0.21 ($p=0.0001$), 0.07 ($p=0.0011$), and 0.15 ($p=0.0001$), respectively (Potter et al, 2001). Originally, the researchers had also inquired about level of concern about tolerance and addiction and found these to be highly correlated with each other and with level of concern about physical dependence. Because of this, the variables for concern about tolerance and addiction were dropped. Therefore, it is assumed that lower level of concern about physical dependence also indicates a lower level of concern about addiction.

More recent graduation from medical school was significant in Models 1 and 2, with R^2 values of 0.04 ($p=0.0025$) and 0.05 ($p=0.0048$), respectively (Potter et al, 2001). Concern about regulatory scrutiny was significant for the second model, explaining 2%

of the variance in willingness to prescribe medications not requiring triplicates on an as-needed basis ($p=0.0424$) (Potter et al, 2001). For the third model, the other two significant predictors were enjoyment in working with chronic pain patients and lower patient case load, with R^2 values of 0.06 ($p=0.0014$) and 0.03 ($p=0.0103$), respectively (Potter et al, 2001).

Additionally, 16% of the respondents indicated that they would never prescribe opioids to someone with a history of substance abuse, 42% would never prescribe opioids to someone currently abusing drugs (Potter et al, 2001). This, coupled with the significant predictor of concern about physical dependence, suggests that a patient's history of substance abuse would affect physician prescribing decisions.

Only 2% indicated that they would never prescribe CIII medications on an as-needed basis, but 35% said they would never prescribe CII medications on a scheduled basis for CNMP (Potter et al, 2001). There also seemed to be differences in willingness to prescribe opioids based on diagnosis, but all of the diagnoses presented were CNMP, and no indication of statistical significance was noted in the article. These findings suggest that the level of control of a substance and diagnosis also affect physician prescribing decisions.

One limitation of this study is the extremely narrow sampling frame used. While the researchers obtained a high response rate of 70% (Potter et al, 2001), only physicians in a small area were chosen to participate in the study, so the generalizability is limited to primary care physicians in the CRN. This is very small number of primary care physicians, as indicated by the sample size of 230, which was the entire population of the

group except for those who were involved in the study itself. Another limitation is found in the design of models 2 and 3. Each model was based on the answer to a single question. Because the question varied on both the level of control of the substance and the dose scheduling, it is impossible to tease out the individual effects that either of these might have alone. Because this study was designed to gather information on prescribing of opioids for CNMP, all of the diagnoses presented were types of CNMP. Although statistical and practical significance of differences found in willingness to prescribe opioids for these conditions was not addressed, the differences were there. If there are differences among diagnoses for the same type of pain, then it is certainly logical to assume that there would also be differences in prescribing decisions for different types of pain being treated.

In the previously mentioned Greenwald survey study, researchers asked a series of questions about the legality and acceptability of prescribing opioids long-term for patients with cancer pain and chronic, non-malignant pain, with and without histories of opioid abuse. For cancer pain, they found that the percentage of respondents finding long-term prescriptions for opioids both lawful and generally acceptable medical practice dropped from 95.4% to 73.8% if the patient had a history of opioid abuse. Likewise, this percentage dropped from 36.9% to 10.5% for chronic, non-malignant pain without and with a history of opioid abuse, respectively. This finding supports the hypothesis that a patient's history of substance abuse could affect prescribing decisions, even for cancer pain.

Weinstein and colleagues also conducted survey about the use of opioid analgesics (Weinstein, Laux, Thronby, Lorimor, Hill, Thorpe, 2000). A 59-item questionnaire was employed to identify how physicians' attitudes and knowledge contribute to pain management practices. Researchers aimed to explore how physician specialty and community size affected practices, and to identify barriers to effective pain management. Medical disciplines identified were psychiatry, internal medicine, surgery/anesthesia, and other. A random sample of physicians practicing in various regions of Texas was drawn from the Texas State Board of Medical Examiners' database. The specific survey methods are not described in detail except to say that there were two mailings of the questionnaire. Three hundred eighty-six physicians responded (Weinstein, et al, 2000). The response rate, however, remains unknown, as the number of questionnaires mailed is not given.

Factor analysis revealed three scales identifying barriers to adequate pain management:

- 1) Reluctance to prescribe opioids (11 items),
- 2) Fear of patient addiction, tolerance, or dependence (5 items),
- 3) Fear of regulatory agency scrutiny (9 items).

Other items measured knowledge about pain and its treatment (13 items), psychological attributes (18 items), and bias about sex and age (5 items). The Likert scale used ranged from 1=Strongly agree to 7=Strongly disagree, so that a low sum score on a scale was

indicative of agreement. For example, a low score on the reluctance scale would indicate that the physician has a high level of reluctance to prescribe opioids.

With regard to physician specialty, no significant differences were found for the three barrier scales, although the authors state that results “approach significance” (Weinstein, et al, 2000). According to the article, the trend is that psychiatrists appear to have lower reluctance and lower fear of patient addiction than the other specialties, and internists tend to have more fear of regulatory scrutiny while surgeons have less. Statistical significance ($p < 0.05$) was achieved on items relating to psychological attributes; the article states that psychiatrists have a more open attitude than other specialties. (Weinstein et al, 2000).

However, when looking at the mean scores, it appears that the results are opposite of the conclusions drawn in the article. For example, the mean score on scale 1 for psychiatrists was 2.81, while the mean score for surgeons was 3.20. Because the scale was defined as 1=Strongly agree and 7=Strongly disagree, this would imply that a lower score indicates agreement with the items. Examining the items on scale 1, only one of them would be reverse-scored. This item was worded “It is appropriate to escalate a dose of narcotics above the usual range if the prognosis is less than 1 year” (Weinstein, et al, 2000). Agreement with other items on this scale appears to indicate higher reluctance. For example, an item is phrased “Narcotics should be restricted to treatment of severe intractable pain” (Weinstein, et al, 2000). Another item is worded “Persons who fit the ‘profile’ of a likely drug abuser should never be treated with narcotics” (Weinstein, et al, 2000). Based on the scale defined by the researchers, agreement with these items would

result in a low score, not a high one. Careful examination of the items on the other scales implies the same. The specific interpretations of results in this article, then, are in question. However, it can be said that in some cases, medical discipline matters, while in others, it does not.

A survey examining benzodiazepine prescribing decisions was conducted by Brown and colleagues to assess the effect of clinical cues on decision making. Also included in the analysis were physician variables such as year of medical school graduation, specialty, clinical interest, and other demographic information. The sample of 226 was drawn from the staff directory at a Midwestern U.S. medical school. Recruitment into participation included two written invitations to schedule interviews, and a written version of the questionnaire sent to non-responders. One hundred and three physicians in various specialties completed the survey via interview, and 13 filled out the written version. Those who answered the written version did not differ in responses from those who completed interviews (Brown, et al, 1997). Medical disciplines represented in this study included: allergy, cardiology, endocrinology, family practice, gastroenterology, general internal medicine, hematology, infectious disease, nephrology, neurology, oncology, psychiatry, pulmonology, rehabilitation, and rheumatology. The highest number of respondents were in family practice (20 respondents), psychiatry (15 respondents), and general internal medicine (13 respondents) (Brown, et al, 1997). Eleven oncologists participated, and the rest of the specialties had 9 or fewer respondents each (Brown, et al, 1997).

A series of 24 patient cases was used to measure physician prescribing of benzodiazepines while varying four factors: health status, psychiatric diagnosis, stability of job and marriage, and short-term ability to work. Additionally, cues such as elevated liver function tests, unstable blood pressure, and esophageal reflux, which along with complaints of nervousness and insomnia can be suggestive of alcohol abuse, were varied in the scenarios. Physician prescribing decisions were measured as level of agreement with continued prescribing of a patient's current therapy, using a scale of -5 (strong disagreement) to +5 (strong agreement), with 0 eliminated in order to force a choice.

The dependent variable was agreement with continued prescribing. Variables of diagnosis and presence of alcohol-related medical problems were found to be significant at the 0.05 level (Brown, et al, 1997). Long-term social stability, recent function, and interaction terms for alcohol-related medical problems with diagnosis were not significant (Brown, et al, 1997). Also in the initial regression model were physician characteristics of year of graduation from medical school and specialty, among others. This study did not find these to be significant with regard to physician prescribing decisions (Brown et al, 1997).

Many medical disciplines were included in this study. However, the patient case scenarios were all about patients presenting specifically with psychiatric complaints. While it is logical to include general practitioners and psychiatrists in this sample, it is unlikely that some of the other specialties, such as allergy/immunology, would be making decisions about prescribing benzodiazepines for these patients. It is unknown whether a

larger sample size with a more focused choice of medical disciplines included might yield different results.

A survey of emergency department physicians also used vignettes to identify factors influencing physicians' decisions to prescribe opioids (Tamayo-Sarver, Dawson, Hines, Cydulka, Wigton, Albert, et al., 2003). The purpose of this study was to determine the effect of patient characteristics and diagnosis on physicians' decisions to prescribe opioids for patients. This was a large survey of 5,750 emergency physicians systematically (every second name) selected from the American College of Emergency Physicians (ACEP) membership list. The survey packet in this study included a cover letter, the questionnaire, and a \$2 bill for incentive (Tamayo-Sarver, et al, 2003). Non-responders were sent a reminder postcard, and then a second questionnaire. The researchers achieved a response rate of 53% (Tamayo-Sarver, et al, 2003). Questionnaires were considered complete enough for analysis if one of the three vignettes was answered. Three models were constructed, one for each of three diagnoses: ankle fracture, migraine, and back pain.

Results showed that the patient characteristic of race/ethnicity was not significant for any of the models; p-values for migraine, back pain, and ankle fracture were 0.65, 0.79, and 0.25, respectively (Tamayo-Sarver, et al, 2003).

In summary, there have been several studies examining factors that affect physicians' prescribing decisions under various conditions. These studies have suggested that level of control of the medication, patient's diagnosis, and patient's history of substance abuse may play a role in physicians' decisions to prescribe controlled

substances. Physician specialty and length of practice may or may not be important, and patient race/ethnicity may not be important. In this study, all of these variables will be put into the initial model except for patient race/ethnicity, which will be held constant.

CHAPTER 3

Preliminary Study

Note: This article will be forthcoming in the Journal of Addictive Diseases.

Overview

This chapter explains a preliminary study of package insert information on drug abuse and dependence. At the time this dissertation was being written, the study had been accepted for publication in the Journal of Addictive Diseases.

Background and Significance

Among the responsibilities of the United States Food and Drug Administration (FDA) is that of ensuring the safety and efficacy of drugs that have a legitimate medical use. Prescriber education is an integral part of facilitating the safe and proper use of medications. The mechanism by which the FDA initially communicates information to health care providers is the FDA-approved product labeling, also called the package insert. The package insert provides information on the risks and benefits of using a particular substance, the approved indications, dosing, pharmacokinetics, side effects, pharmacology, contraindications, warnings, and precautions. Abuse and dependence potential of a drug is also included in this information. Prescription drug abuse is an ongoing problem in the United States (Jongston, O'Malley, Bachman, Shulenbert, 2004;

Mohler-Kuo, Lee, Wechsler, 2001). Because the FDA's initial communication of drug information to prescribers is through the package insert, it is imperative that the drug abuse and dependence information contained in these package inserts use clear and consistent language in order to be clinically useful.

Scientists have long debated the definitions of addiction, abuse, and dependence. Numerous review and opinion papers propose definitions and appropriate use of the words, and committees have been formed in an effort to standardize terminology (Dodes, 1996; Maddux and Desmond, 2000; Peele, 1977; Goodman, 1990; Savage, Joranson, Covington, Schnoll, Heit, Gilson, 2003; Trachtenberg). Use of these terms, however, continues to be an issue. A qualitative assessment of information about opioid use and addiction potential in fourteen textbooks was performed by Ferrell et al. They found that information, based on the researchers' definition of "addiction," was more often inaccurate than not, and highly varied in how "addiction" was defined and used (Ferrell, McCaffery, Rhiner, 1992).

Considering the history of inconsistent use of terminology related to substance abuse and dependence, variability could be carried over into physician opinions. In a survey of 500 physicians, researchers gathered data about general knowledge of practitioners in the area of pain management, including the definition of "addiction" and legal issues associated with prescribing controlled substances. Survey respondents defined addiction in a variety of ways even when it was presented as a multiple choice question (Greenwald, Narcessian, Pomeranz, 1999).

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) does not use the word “addiction,” but instead gives criteria for “substance abuse” and “substance dependence,” respectively (American Psychiatric Association, 2000). Both are described as maladaptive patterns of substance use, the symptoms of which differ slightly in intensity and nature.

The discrepancies in definitions for addiction, dependence, and abuse and usage among textbooks and the primary literature could potentially carry over into product labeling (package inserts). This can lead to differences of opinion among prescribing physicians about a drug’s potential for abuse or dependence and influence prescribing decisions. Other health care professionals (e.g., pharmacists, nurse practitioners) also interpret package insert information. Variability in definitions and usage can affect both prescribing and patient counseling information.

No published systematic evaluations of abuse and dependence potential information in package inserts were found in a Medline search. There have been studies of other categories of information in product labeling (e.g., pregnancy, hepatotoxicity) all of which revealed deficiencies in the information in question (Uhl, 2002; Spyker, Harvey, Harvey, Abernathy, 2000; Hung, Ponto, Gadiant, 2004; Willy, Li, 2004; Mullen, Anderson, Kim, Blanc, Olson, 1997). One such study reported that only 11% of a sample of over 100 pregnancy category X drugs contained, beyond a box warning or contraindication for use in pregnancy, specific risk management strategies such as obtaining negative pregnancy tests before initiation and during drug therapy (Uhl 2002).

A study by Spyker et al. assessed clinical pharmacology information in 76 package inserts from the 1996 edition of the Physicians' Desk Reference (PDR). Researchers in this study created a scale for the evaluation of the information and assigned each package insert a percentage score for containing predetermined information, such as identification of the active agent, its mechanism of action, and duration of effect. The authors reported a median percentage score of 31% and concluded that package inserts are deficient in clinical pharmacology information (Spyker et al., 2000).

Hung et al. identified five categories of problematic instructions in the package insert information for the preparation of radiopharmaceuticals: absent or incomplete, restrictive, inconsistent, impractical, and vague directions. These researchers concluded that the information provided in FDA-approved product labeling should be considered guidance and not a requirement, and that nuclear pharmacists and physicians should be able to deviate from the methods provided in the package insert (Hung, et al, 2004).

Another study of FDA-approved product labeling examined the consistency and quality of information about hepatotoxicity for 95 prescription drugs from the 2000 PDR with a checklist used to create an informativeness score. The mean informativeness score was 35% and the authors concluded that information provided in labeling is variable but may be improved by increasing consistency of information on hepatotoxicity in the product labels (Willy, Li, 2004).

A comparison of overdose management information found in the PDR to toxicology references indicated that there are deficiencies in PDR overdose treatment

strategies. The authors report that almost half of the evaluated PDR entries recommended either ineffective or contraindicated therapies (Mullen et al., 1997). This study draws attention to the possibility of clinically inaccurate information in package inserts.

Objective and Hypotheses

Based on the historical lack of consensus on the use of drug abuse and dependence-related terminology and the inadequacy of package insert content suggested by prior reviews thereof, an evaluation of the drug abuse and dependence information in package inserts was conducted. The purpose of this project was to describe and evaluate package insert content with regard to abuse and dependence potential for drugs that are dispensed in community pharmacies. Package inserts for products in higher controlled substance schedules (those with lower schedule numbers which have higher abuse potential) should have stronger warnings and more information about drug abuse and dependence than those products with less abuse potential.

Methods

The American Hospital Formulary System (AHFS) 2003 was used to identify drugs that act in the central nervous system (CNS). The following CNS-active drug classes were selected:

- Analgesics and anti-pyretics: opiate agonists and partial agonists

- Anticonvulsants: barbiturates and benzodiazepines
- Anorexigenic agents, respiratory stimulants, and cerebral stimulants
- Anxiolytics, sedatives, and hypnotics: barbiturates, benzodiazepines
- Miscellaneous central nervous system agents

Drugs in these classes were then cross-referenced with the 2003 Electronic Physicians' Desk Reference (E-PDR) (AHFS, 2003, Medical Economics Company, 2003). Drugs with brand names and full package inserts were included in the study. Generic products and injectable preparations were excluded. A full list of package inserts included in the study is included as Appendix A of this document.

Microsoft Access™ was used to create a database. The drug's generic and brand name, manufacturer, Federal Controlled Substance Act (CSA) schedule, and AHFS therapeutic classification were recorded. Package inserts in the E-PDR were reviewed by one researcher (LBP). Information pertaining to drug abuse and dependence was then extracted into the database.

In the first part of the study, each package insert was evaluated for content. The main parameter assessed was the presence or absence of primary terms: addiction, dependence, physical dependence, and psychological or psychic dependence. Also noted was the presence or absence of other terms: habituation or habit-forming, tolerance, withdrawal, abstinence syndrome, drug-seeking behavior, misuse, abuse, diversion, craving, and illegal or illicit use.

A coding system was then created to further describe how the above terminology was used in the package insert. For example, it was noted whether or not the term was described or defined in the package insert. The strength of the warning about abuse potential was subjectively assessed for each package insert. If the phrase “may cause dependence” was used, the warning was considered mild. Statements that the drug “has been abused” or “has caused dependence” indicated a moderate warning. Strong warnings about abuse potential were marked by phrases such as “actively sought out by drug abusers, diversion not limited to those with a history of substance abuse”, and the words “severe” or “extensive” being used to describe dependence on the drug. Other codes included: the presence or absence of terminology indicating either evidence of no abuse or dependence potential or lack of information about abuse or dependence potential, the presence or absence of warnings regarding tapering of doses or consequences of abruptly stopping medication, and the presence of an entire section designated for abuse and dependence information. A complete list of codes and their meanings is available as Appendix B of this document. The number of sentences dedicated to information about abuse and dependence potential was recorded as a method of quantifying the amount of information in the package insert related to drug abuse or dependence.

Descriptive statistics were used to characterize the data. Frequencies were reported for parameters recorded as present or absent. Central tendency and spread of the amount of information relating to drug abuse and dependence was quantified by median and range for number of sentences since the data were not normally distributed. Kruskal-

Wallis was used to compare the amount of information across schedules for controlled substances (CII-V) and across warning strength categories. Spearman's Rho correlation was used to determine strength and significance of time trends in the amount of information using the original drug approval date and the date of the last label revision because the data for these continuous variables were not normally distributed.

Results

Of the 77 entries in the package insert database, 40 were opiate agonists, 18 were stimulants, and the remainder fell into one of the following categories: opiate partial agonists, anticonvulsants, anxiolytic/sedative/hypnotics, or miscellaneous CNS agents. Twenty-nine records were in schedule II, 24 in schedule III, 15 in schedule IV, 1 in schedule V, and 8 were non-scheduled. Table 3.1 shows the number of package inserts in each AHFS class and each Federal Controlled Substance Act schedule (CSA schedule).

Table 3.1 Frequency of package inserts included in study of drug abuse and dependence warnings as a function of AHFS classes and CSA schedules

AHFS Class / Federal Controlled Substance Act Schedule	CII	CIII	CIV	CV	NS	Total
Analgesics: Opiate Agonists	18	18	1	1	2	40
Analgesics: Opiate Partial Agonists	0	0	3	0	0	3
Anticonvulsants: Barbiturates	0	0	0	0	1	1
Anticonvulsants: Benzodiazepines	0	0	1	0	0	1
Anorexigenics, Respiratory & Cerebral Stimulants	11	2	4	0	1	18
Anxiolytics, Sedatives, Hypnotics: Barbiturates	0	3	0	0	1	4
Anxiolytics, Sedatives, Hypnotics: Benzodiazepines	0	0	4	0	0	4
Anxiolytics, Sedatives, Hypnotics: Miscellaneous	0	0	2	0	3	5
Miscellaneous CNS agents	0	1	0	0	0	1
Total	29	24	15	1	8	77

Of the eight non-scheduled products, two were opiate agonists (tramadol), five were anxiolytic/sedative/hypnotics (phenobarbital [2], hydroxyzine [2], promethazine [1]), and one was a stimulant (caffeine).

Table 3.2 shows the frequencies of a section designated specifically for information about drug abuse and dependence for each AHFS class and CSA schedule.

Table 3.2 Frequencies of sections specifically dedicated to information about drug abuse and dependence for each AHFS class and CSA schedule

Class	# Inserts	Percentage
Opiate Agonists	37/40	92.5
Opiate Partial Agonists	3/3	100
Anticovulsants: Barbiturates	0/1	0
Anticonvulsants: Benzodiazepines	1/1	100
Stimulants	14/18	77.8
Anxiolytic, Sedative, Hypnotics: Barbiturates	¾	75
Anxiolytic, Sedative, Hypnotics: Benzodiazepines	¾	75
Anxiolytic, Sedative, Hypnotics: Miscellaneous	2/5	40
Miscellaneous CNS agents	1/1	100
Total	64/77	83.1
Schedule		
CII	25/29	86.2
CIII	24/24	100
CIV	12/15	80
CV	1/1	100
Non-scheduled	2/8	25
Total	64/77	83.1

About 83% of the 77 package inserts had a section dedicated specifically to drug abuse and dependence information. Most opiate agonists and stimulants had a dedicated section for drug abuse and dependence information. There was a dedicated section for

drug abuse and dependence information in 100% of the inserts in CSA schedules III and V, although there was only one schedule V insert.

Table 3.3 shows the frequencies of package inserts in each AHFS class and CSA Schedule containing primary terminology.

Table 3.3 Appearance of primary abuse and dependence-related terminology in package inserts from AHFS classes and CSA schedules

Class	Addiction	Dependence	Physical Dependence	Psychological Dependence	Abuse
Opiate Agonists	13	25	39	36	29
Opiate Partial Agonists	0	2	3	2	3
Anticovulsants:	0	0	0	0	0
Barbiturates					
Anticonvulsants:	1	1	0	0	0
Benzodiazepines					
Stimulants	1	14	2	16	17
Anxiolytic, Sedative, Hypnotics:	2	1	3	3	3
Barbiturates					
Anxiolytic, Sedative, Hypnotics:	1	4	4	4	1
Benzodiazepines					
Anxiolytic, Sedative, Hypnotics:	2	2	1	0	2
Miscellaneous					
Miscellaneous CNS agents	0	1	0	0	1
Total:	20	50	52	61	56
Schedule					
CII	11	24	18	26	27
CIII	4	13	21	22	15
CIV	5	11	10	10	11
CV	0	1	1	1	1
NS	0	1	2	2	2
Total	20	50	52	61	56

The word “addiction” appeared in 26% of the 77 records (13/20 were opiate agonists). The word “dependence” without distinction for physical or psychological was found in 65% of the 77 records (25/50 were opiate agonists, 14/50 were stimulants). Of the primary terms, “psychological dependence” appeared most frequently (61/77 inserts). However, terms frequently associated with the concept of psychological dependence, such as craving and drug-seeking behavior, appeared only rarely (3 and 7 inserts, respectively). The frequencies for presence of other terms are found in Table 3.4. The two most commonly used of the other terminology were “tolerance” and “withdrawal.”

Table 3.4 Appearance of other abuse and dependence-related terminology in package inserts

Term	Number of Package Inserts (n=77)	Percentage (%)
Tolerance	60	77.9
Craving	3	3.9
Withdrawal	53	68.8
Abstinence Syndrome	14	18.2
Misuse	16	20.8
Diversion	4	5.2
Habit-forming/Habituation	25	32.5
Illicit/Illegal Use	2	2.6
Drug-seeking Behavior	7	9.1

Warning strengths are summarized for each AHFS class and CSA Schedule in Table 3.5.

Table 3.5 Strength of warnings about drug abuse and dependence appearing in each AHFS class and CSA schedule

Class	Strong	Moderate	Mild	Total
Opiate Agonists	3	10	27	40
Opiate Partial Agonists	1	2	0	3
Anticovulsants: Barbiturates	0	0	1	1
Anticonvulsants: Benzodiazepines	0	0	1	1
Stimulants	7	9	1	17*
Anxiolytic, Sedative, Hypnotics: Barbiturates	0	3	1	4
Anxiolytic, Sedative, Hypnotics: Benzodiazepines	0	2	2	4
Anxiolytic, Sedative, Hypnotics: Miscellaneous	0	0	2	2*
Miscellaneous CNS agents	1	0	0	1
Total	12	27	34	73*
Schedule				
CII	6	12	11	29
CIII	2	7	15	24
CIV	2	7	6	15
CV	0	1	0	1
Non-scheduled	2	0	2	4*
Total	12	27	34	73*

*The package inserts that had no warning about drug abuse were all non-scheduled; one for caffeine, 1 for promethazine, and 2 for hydroxyzine.

Of those inserts with mild warnings, 88.2% were opiate agonists. Of those with strong warnings, 58.3% were stimulants, 33.3% were opiate agonists (2/4 were non-scheduled), and 8.3% (1 insert) was an opiate partial agonist. The strongest warnings appeared in cerebral stimulants and opiate agonists; however, the strength of warnings within AHFS classes was variable, particularly for the opiate agonists. Many of the schedule II opiate agonists had mild warnings while two of the four opiate agonist/partial agonist products with strong warnings were non-scheduled (both contain tramadol). Strength of warning was not significantly different across CSA schedules ($p=0.069$), nor did it have any correlation with original approval date ($p=0.610$).

Eighteen (23.4%) package inserts indicated that abuse, dependence, or addiction was rare. All but one of these 18 were opiate agonists. Thirteen said that “dependence” was rare, and 5 stated that “addiction” was rare. The two that asserted “abuse” was rare also stated that “dependence” was rare.

A boxed warning about drug abuse and dependence appeared in 51.7% of the schedule II drug records. The percentage of records with boxed warnings in the remaining schedules was less than 15% each.

The overall median number of sentences on drug abuse and dependence was 17 with a range of 0-66. The greatest variability was found among the opiate agonists (median 20, range 7-66 sentences). There was high variability in all schedules except schedule V, in which there was only one entry (14 sentences). Table 3.6 shows the median and range of sentences found in each CSA Schedule.

Table 3.6 Number of sentences about drug abuse and dependence in each CSA schedule

Schedule/Number of Sentences	Number of Sentences: Median (Range)
CII	15 (5-66)
CIII	19 (9-48)
CIV	15 (7-62)
CV	14 (only one package insert was a CV)
Non-scheduled	1 (0-28)

The amount of information in controlled substances (scheduled II-V) did not significantly vary across CSA schedule ($p=0.443$), nor was it significantly different across warning strength categories ($p=0.821$). There was a positive significant

correlation between the number of sentences and the original drug approval date (Spearman's $\rho=0.429$, $p<0.001$). On the other hand, the correlation between the number of sentences and year of most recent label revision was not significant (Spearman's $\rho= -0.040$, $p=0.749$).

Discussion

Variability in information about drug abuse and dependence potential is high and can be confusing for health care professionals. Neither the strength of warning nor the amount of information dedicated to drug abuse and dependence significantly differed across CSA schedules, indicating that neither the amount of information on drug abuse and dependence nor the strength of the warning accurately reflects the CSA schedule into which a drug falls. For example, two inserts with strong warnings and a moderate amount of information (21 and 28 sentences, respectively) were non-scheduled. The warnings and amount of information in these cases seem to contradict the implication that the drug has little to no abuse liability based on its non-scheduled status. An explanation for the lack of relationship between warning strength and schedule control would be an overall increase in warning strength over time; however, original approval date did not correlate with warning strength.

The sample of inserts in this study is heavily weighted toward opiate agonists, with stimulants being the second largest group. While most package inserts explain or describe physical dependence, tolerance, and withdrawal, there is a lack of information about psychological dependence, which was the most frequently appearing of the primary

terms. The word “addiction,” which is not universally defined and does not appear in the DSM-IV-TR, is frequently used. Many words commonly associated with the idea of psychological dependence and addiction, however, are rare.

The stimulants had stronger warnings and more boxed warnings about drug abuse and dependence than did opiate agonists. Not surprisingly, however, the opiate agonists had more information about physical dependence, tolerance, and withdrawal; however, twelve opiate agonist package inserts indicated that “dependence” was rare.

The amount of information, quantified by the number of sentences, is also highly varied, even within package inserts for the same drug. For example, there were six entries for products containing oxycodone, and the number of sentences about drug abuse and dependence ranged from 7-66. For morphine, six entries ranged from 9-46 sentences.

The amount of information on drug abuse and dependence increased over time with respect to the original approval date of the drug, but not the date of the latest label revision. It is possible that the overall length of package inserts has also increased over time as approval requirements for detailed information also increase. Thus, it is possible that the proportion of total package insert information related to drug abuse and dependence information has not changed; however, this remains unknown as the overall length of the package inserts was not collected in this study.

There are several limitations to this study. The E-PDR was the only source of package inserts used and only brand named drugs were included. Because manufacturers pay to have information published in the PDR, the content changes from year to year.

Consequently, a sample using the same selection criteria with a PDR from another year could yield a different number of package inserts and distribution of schedules and classes. Likewise, the package inserts themselves may have been revised and differ from those collected in this data set in 2003. As a result, the sample of package inserts included in this study may not be representative of all of the drugs currently on the market.

Although objective criteria were applied in the determination of warning strength, it was highly subjective, and only one person evaluated the package inserts. Finally, the sample of package inserts used here was heavily weighted towards opiate agonists, with very few drugs in some of the other AHFS classes. This makes it difficult to draw generalized conclusions about those classes with very few package inserts. The same holds true for CSA Schedules; well over half of the package inserts were in schedules II and III, making it difficult to draw conclusions about variability within the other schedules.

Conclusion

Evaluation of 77 package inserts for CNS-active drugs demonstrated high variability in terminology related to drug abuse and dependence. The confusion generated by this inconsistency can affect prescribing decisions of currently practicing physicians, patient counseling by pharmacists and other health care professionals, and the education materials that students in the health care arena receive. Consequently, the ambiguity and complexity of understanding drug abuse and dependence and its treatment is perpetuated.

The inconsistency found in this study indicates that package inserts are not a clinically useful source of information about abuse and dependence liability of prescription drugs in the U.S. It then becomes important to determine if this variability also appears in health care provider's opinions about the utility of information provided in package inserts, and to discover what sources of information are used to gain knowledge about abuse and dependence potential of prescription drugs. If, for example, the CSA schedule itself is significantly important to health care providers, this places great importance on the application of scientific information available when assigning schedule control during the approval process (Balster and Bigelow, 2003). Until standardized, common language is in place, this variability will continue and perpetuate confusion about drug abuse and dependence. It is imperative to develop common language for use in package inserts to improve communication about abuse and dependence potential of prescription drugs and further attempt to prevent prescription drug abuse.

CHAPTER 4

Methods

Overview

This chapter describes the methods used to meet the objectives stated in Chapter 1. After the objectives are restated and briefly addressed, details of the sampling frame and scope of the project, the development and piloting of the questionnaire, the survey process, and data analysis are presented.

Summary of Objectives

Objective 1: Describe how physicians define the terms drug dependence and addiction.

Physicians were asked to choose factors they felt were necessary for the clinical states of drug dependence and addiction to exist. Frequencies were reported for descriptive purposes.

Objective 2: Characterize sources used by physicians for drug abuse and dependence and other drug information.

Physicians were asked to indicate how frequently they used various sources for drug abuse and dependence information and other drug information.

Mean values for these were calculated for the purpose of more accurately ranking the sources physicians consult.

Objective 3: Portray the scope of the problem of varied terminology in package inserts by characterizing its effects on physician prescribing decisions when modeled with covariates of physician and patient characteristics.

Physicians were presented with a series of four case scenarios with package insert excerpts representing a medication given to the patient. Physician prescribing decisions were measured as comfort level with a prior physician's choice, likelihood of refilling the prescription, and likelihood of choosing the drug if the respondent was the first physician to see the patient. Additionally, physicians rated how useful they find a particular package insert excerpt to be in making a clinical decision.

For physician, patient, and package insert characteristics, regression models tested whether coefficients were equal to zero. Interactions for the variables history of substance abuse with type of pain and strength of warning were tested for coefficients of zero as well.

Objective 4: Provide groundwork for research designed to evaluate and develop more useful package inserts.

Areas for future research are discussed in Chapter 6.

Sampling Frame and Scope

The sampling frame consisted of physicians currently licensed and residing in the Commonwealth of Virginia as of October 2005. At the time the study was started, there were 34,694 physicians with M.D. or D.O. degrees in the Virginia Department of Health Professions database, available online at <http://www.vahealthprovider.com/search.asp>. A database containing each physician's name, primary practice address, license number, date of issue, expiration date, specialties, and degree (M.D., D.O., Intern/Resident) was created in Microsoft Access. Of the 34,694 physicians, 21,835 had Virginia addresses, and 797 had licenses that were expired. There were 4,635 intern/residents. Those with generalized specialties numbered 14,411.

Inclusion/Exclusion Criteria

Doctors of Osteopathy were included in the sampling frame as they have full prescribing power. Interns and residents were excluded since they do not yet have complete autonomy in decision making. Because of the nature of the patient cases depicted in the questionnaire, only generalized specialties most likely to see the patients presented were included in the sampling frame. Those specialties included were: general practice, family practice, internal medicine, emergency medicine, public health, and preventative medicine.

Sample Size

The required sample size for a margin of sampling error of (5% for the population size of 14,411 was 375. Based on a predicted response rate of 25-30%, 1248-1500 physicians were needed in order to yield the sample size. Equation 1 was used for this calculation.

$$N_s = \frac{N_p p(1-p)}{(N_p - 1) \left(\frac{B}{C}\right)^2 + p(1-p)} \quad (1)$$

In the above equation, N_s is the required sample size, N_p is the population size, p is the proportion of the population expected to choose one of a two-response item, B is the acceptable amount of sampling error, and C is the z-statistic associated with the chosen confidence interval (Dillman, 2000). For this project, p was assumed to be 0.5, the lowest variability in responses, which would increase the needed sample size. An accepted error rate of +/-5% was used, and 1.96 was used as the z-statistic corresponding with a 95% confidence interval. Because of budget and labor constraints, however, a random sample of 1008 physicians was used, so that equal numbers of each of the 24 versions of the questionnaire were sent out.

The random sample is expected to reflect the population of actively licensed physicians in general practice areas in the Commonwealth of Virginia with respect to demographics and generalizability of results.

Development of Questionnaire

The questionnaire was designed to gather information on physicians' prescribing decisions, opinions about package insert excerpts, sources used for drug information, ideas about addiction and drug dependence, and various demographics. The questionnaire presented physicians with four patient cases, each associated with a different package insert excerpt, and a series of five questions related to each case. The final section was designed to ascertain information on sources used for drug information, the importance of certain factors in making prescribing decisions, ideas about drug dependence and addiction, and to obtain demographic information. A complete version of the final questionnaire can be found in Appendix C.

Section 1: Patient Case Scenarios

The first section of the questionnaire presented physicians with four patient case scenarios and a package insert excerpt. Patient case scenarios were used to indirectly assess how various patient characteristics might also influence prescribing decisions. Patient characteristics included the type of pain and history of substance abuse.

The first patient characteristic was the type of pain being treated. The four levels for type of pain were:

- 1) Acute, represented by a recent broken ankle,
- 2) Chronic, malignant/cancer pain,
- 3) Chronic non-malignant pain of known origin (CNMK), represented by osteoarthritis, and

- 4) Chronic non-malignant pain of unknown origin (CNMU), represented by lower back pain of unknown etiology.

Levels for pain type were initially acute and chronic. However, chronic pain cannot easily be represented by one condition, so three levels for chronic pain were defined. Common complaints were chosen to represent chronic, non-malignant pain conditions.

The second patient characteristic varied in the case scenarios was history of substance abuse. There is a wide spectrum of substance abuse history possible. The length of time since a person has used, whether or not they are in a controlled environment, extent of use, type of substance/s used, and relapse can all affect a physician's view of the risk of abuse for a patient. However, this was not the focus of this study, and in order to maintain a reasonable number of variables, the patient's history of substance abuse was represented by one of three levels:

- 1) Current, described as occasional use for recreational purposes
- 2) Past, indicated by a previous use but not within the last 5 years,
- 3) No history of substance abuse.

Because patient demographics were not variables of particular focus in this study, the patient's age, sex, and ethnicity were kept constant. This also kept the number of variables at a more manageable level. Based on United States Census Bureau information from 2000, the patient was a 38 year-old Caucasian male. The four levels of pain type and three levels of substance abuse history required a total of twelve patient case scenarios in order for all combinations to be used. The patient case scenarios used in the final questionnaire versions are available as Appendix D. A package insert excerpt

representing a medication previously prescribed to the patient followed each case scenario. Package inserts contained three variables:

- 1) Warning strength, classified as either “strong” or “not strong,”
- 2) Advice, which was either present or not present,
- 3) Definitions of terminology used in the package insert, also considered either present or not present.

Each package insert was classified on these variables a priori independently by three researchers (LBP, PWS, SEH). Strength of warning was initially classified as “mild, moderate, or strong” but later collapsed into two categories. Initially, definitions were counted, but this was also collapsed into two categories of “present” and “not present.”

Criteria for classification were as follows:

- 1) Strength of the warning: Specifically, the statement regarding the dependence potential of the drug.

Mild: Groups the drug in question with other drugs, taking focus off the drug itself. Looked for phrases such as: "Drugs in this class have been associated with dependence" "Like other drugs in this class, Drug X may cause dependence"

Moderate: Implicates the drug itself as the cause of dependence, but does not indicate any severity. Phrases include "Drug X has been associated with dependence" "Drug X can cause dependence"

Strong: Implicates the drug at hand with severe or debilitating dependence, or has high dependence potential. Phrases include "Drug X has been associated with severe dependence" "Drug X can cause dependence resulting in severe/debilitating social/occupational dysfunction" and the like.

- 2) Direct advice given: Evaluates whether or not the information tells a physician what to do in a specific situation.

Yes: The information uses the imperative/command form of a verb. For example "Do this in this situation" or "Do not do thus and so"

No: No direct advice given. This includes "suggestions" that do not directly tell a physician what to do. For example, "Those with a history of substance abuse may be at higher risk for psychic dependence", "Withdrawal symptoms may occur if the drug is discontinued abruptly" or "Symptoms of withdrawal may be relieved/caused by administration of..."

- 3) Definitions: Evaluation of definitions for terminology of interest. A "point" is given for each term defined or described. Terms include: addiction, drug dependence, physical dependence, psychic/psychological dependence, tolerance, and withdrawal.

Based on three variables with two levels each, eight package insert excerpts were used to include all possible combinations. The finalized versions of the package insert excerpts are detailed in Appendix E of this document.

As described above, twelve patient case scenarios and eight package insert excerpts were used. In order to ensure that all 96 combinations of patient case scenarios and package inserts were used, 24 versions of the questionnaire, each with four different combinations, were created. Each questionnaire version contained a patient case with each type of pain, and at least one each of the three levels of substance abuse history. Likewise, each version had at least one strong warning, at least one package insert containing advice, and at least one package insert with definitions of terminology. A 4-point Likert scale was used with points labeled "not at all, not very, somewhat, and definitely." Survey respondents tend to gravitate toward middle responses (Dillman, 2000). Because the questions asked here were thought more likely to cause indecision, which would render those responses useless for data analysis, a neutral response was not provided as an option.

In addition to the three measures of prescribing decisions, physicians were asked two additional questions at the end of each scenario about the package insert excerpts to assess physician-rated usefulness and warning strength. The first was how useful the package insert information was, and was measured with the same Likert scale described above. The second question asked physicians to classify which Controlled Substance schedule was most appropriate for the drug.

Section 2: Sources Consulted for Drug Information

Information on sources used for drug information was presented as a grid, where physicians were to select how often they used various sources for drug abuse and dependence information and for other information. Figure 4.1 shows the grid used.

Figure 4.1 Grid used for gathering information about sources consulted by physicians

Please indicate how often you consult the following sources for drug information. The shaded column is for drug abuse and dependence information, and the unshaded column is for other information.

Source Consulted	Never	Yearly	Monthly	Weekly	Daily
Direct contact with manufacturer					
Drug Information Center					
Internet Source					
Package Insert					
Personal Digital Assistant (PDA)					
Pharmacist					
Physician's Desk Reference (PDR)					
Other					

Section 3: Factors in Clinical Decision-Making

In this section, physicians were overtly asked to rate the importance of various factors in their clinical decision-making. The factors represented the patient and package insert characteristics presented in the patient case scenarios. They were:

- 1) Controlled Substance schedule,
- 2) Definitions of terminology provided in the package insert,
- 3) Patient's history of substance abuse,
- 4) Presence of clinical advice in package insert information,
- 5) Type of pain being treated,
- 6) Warning strength in package insert information.

A 4-point Likert scale with points labeled “not at all important, somewhat unimportant, somewhat important, and very important” was used. Again, no neutral response option was provided.

Section 4: Definitions of Addiction and Drug Dependence

To characterize how physicians perceive the terms “addiction” and “drug dependence,” a list of seven possible symptoms or conditions was presented. These were:

- 1) Abuse,

- 2) Craving,
- 3) Drug-seeking behavior,
- 4) Physical dependence,
- 5) Psychological dependence,
- 6) Tolerance,
- 7) Withdrawal.

Physicians were asked to choose which were necessary for drug dependence to exist, and again for addiction. Respondents could choose all that apply.

Section 5: Demographic Information

Demographic information collected included physician gender, initial year of licensure, medical specialty, estimated percentage of patients with a known history of substance abuse, and region of practice. Initial year of licensure, medical specialty, and estimated percentage of patients with a known history of substance abuse were open-ended to allow for more specific data collection. Region of practice was presented as a list of eight areas corresponding with zones indicated on a map of Virginia. The regions were labeled:

- 1) Northern,
- 2) Western,
- 3) Central,
- 4) Tidewater,
- 5) Southern,

- 6) Southwestern,
- 7) Northern Neck,
- 8) Eastern Shore.

Pilot of Questionnaire

The development and pre-testing of the questionnaire occurred in the following stages:


- 1) Review by committee: The review committee consisted of the five members of the dissertation advisory committee plus one other survey researcher and a practicing primary care physician. This committee, consisting of experts in the areas of substance abuse research, survey methodology, clinical research, and practice, allowed for feedback from a diverse background of expertise.
- 2) Survey feedback: A convenience sample of 5 physicians who agreed to the task was asked to fill out the questionnaire and provide feedback upon completion. This feedback was used to further polish the items and format of the questionnaire. Responses on these questionnaires were not recorded for use in the data analysis of the final survey, as the purpose of the procedure was to gain insight into the strengths and weaknesses of the questionnaire itself. Comments received by these physicians are provided in Appendix F of this document.
- 3) Final review by committee: A final review by the dissertation committee was used to uncover typographical errors, incorrect numbering, and any other previously overlooked mistakes before mailing occurred.

- 4) Cover letter: A cover letter explaining the general purpose of the survey and stressing the importance and appreciation of response and assuring anonymity was written and approved by the committee. The finalized cover letter for the first mailing is represented as Appendix G of this document.
- 5) In order to easily distinguish between versions of questionnaires upon return, four different colors of paper were used for the covers, and six combinations of location for the correspondence address and VCU Medical Center logo were used.

Survey Process

After approval was granted by the Institutional Review Board (IRB), the Tailored Design Method suggested by Dillman (2000) was implemented. This method involves multiple contacts to the selected sample of physicians and has been shown to increase response rate (Dillman, 2000). Each of the randomly selected physicians was assigned a number from 0001 to 1008. There were a total of four contacts. The first mailing packet contained four items: a cover letter, a questionnaire, a stamped, addressed return envelope, and a response postcard. The postcard, shown in Figure 4.2, included just the physician's code number and check boxes stating, "I have completed and returned the questionnaire," and "I do not wish to participate in this survey." This postcard was also stamped and addressed for ease of mailing. The cover letter and questionnaire instructions indicated that the postcard was to be returned separately from the questionnaire.

Figure 4.2 Return postcard


 Regarding the
Drug Abuse and Dependence Survey

Please check the appropriate box below and return this card so that you may be removed from the mailing list.

Name: _____

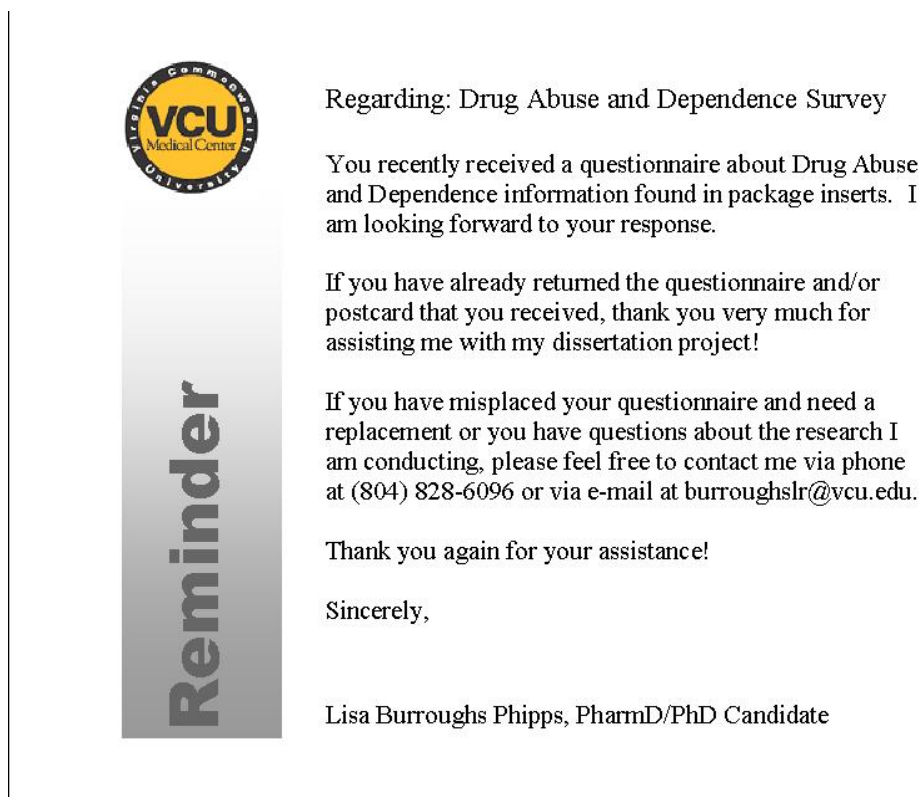
I have filled out and returned the questionnaire.

I do not wish to participate in this survey.

The separate mailing of the questionnaire and the postcard both maintained total anonymity and allowed for tracking of respondents. Physicians who mailed the return postcard did not receive a replacement questionnaire in the third mailing, as described below.

The second mailing occurred two weeks after the questionnaire packet was mailed. A reminder/thank you postcard, shown in Figure 4.3, was sent to each physician with the exception of refusals (i.e., those who had returned the postcard with the box checked next to “I do not wish to participate in this survey”) and to whom the initial mailing was returned as undeliverable.

Figure 4.3 Thank you/reminder postcard



This postcard thanked those who completed the questionnaire and served as a reminder to those who had not yet responded.

The third mailing was sent three weeks later to those who had not yet responded and included a revised cover (Appendix H) letter and replacement questionnaire was sent to those who had not yet responded. The fourth mailing was another reminder/thank you postcard sent another three weeks later. This technique of multiple contacts was employed to improve response rates as discussed by Dillman (2000).

Data Entry and Analysis

Questionnaires were opened in batches of 10 or more at a time so that no postcard returned could be matched with a questionnaire, further maintaining anonymity.

Questionnaires returned more than 4 weeks after the final mailing were not used in data analysis. As postcards were returned, the matching entry in the database was coded with a “Y” for those who responded, an “N” for those who indicated they did not wish to participate in the survey, and an “R” for those returned as undeliverable.

SPSS for Windows 13.0 statistical software was used to analyze the data. A questionnaire was considered complete if at least three of the patient cases were answered and if responses were provided for sections 2, 3, 4, and at least 3 of the 5 questions in section 5. Sections 2-5 consisted of the information about sources used for drug information, importance of factors in making clinical decisions, definitions of addiction and drug dependence, and demographics.

Categorical variables were coded as numbers, while numerical variables were recorded directly. Indicator variables were created for categorical variables with more than two categories. The codebook is available as Appendix I of this document.

Region of practice was collapsed into three categories: Southwestern, urban, and other rural. Southwestern Virginia was used as the reference group because it was a region of interest. Physician specialty or medical discipline was collapsed into four categories: family practice, internal medicine, emergency medicine, and other.

Emergency medicine was used as the reference group for this set of indicator variables.

For type of pain, chronic, non-malignant pain of unknown etiology (CNMU) was the

reference group because the other types of pain had a known cause. For substance abuse history, “none” was the reference group as the other levels of the variable represented at least some history of substance abuse.

Interaction terms were created for three sets of variables: history of substance abuse with type of pain, history of substance abuse with warning strength, and type of pain with warning strength. Because the indicator variables were used to create the interaction products, there were a total of 11 interaction products entered into the model: six representing history of substance abuse with type of pain, two representing history of substance abuse with warning strength, and three representing type of pain with warning strength. These were added into the model in three separate blocks.

Demographic information was characterized using descriptive statistics as appropriate. Frequencies were reported for categorical variables of gender, specialty, and region of practice. For the continuous variables of initial year of licensure and percentage of patients with a known history of substance abuse, mean and standard deviation or median and range were used as determined by normality.

Frequencies were reported for the terms physicians associated with drug dependence and addiction, and for sources used for drug information.

Missing data:

Fortunately, the large majority of questionnaires returned were filled out completely enough for analysis. Because of the small numbers of missing data on each variable, the following techniques were used to deal with missing data:

- Initial year of licensure was replaced with the median
- Sources grid: For the grid concerning sources used for drug information, it was assumed that missing data were indicative of a “never” response, and was therefore transformed in SPSS from “system missing” to “0.”
- For case scenario questions: case scenarios left unanswered were dropped.

Regression Models

Linear regression models were used to describe the effect of the physician, patient, and package insert characteristics on physician prescribing decisions. Four models were evaluated, one for each of the prescribing decision measures, and one for a sum scale measurement for willingness to prescribe. The last would be evaluated only if the three individual measures were highly correlated with each other and had a reliability of $\alpha \geq 0.7$.

The major dependent variable was a decision to prescribe medication. This was measured in three ways:

- 1) Comfort level with a prior physician’s choice
- 2) Likelihood of refilling the prescription
- 3) Likelihood of choosing the drug if the respondent was the first physician to see the patient.

Each model is represented by equation 2:

$$\hat{Y} = B_1X_1 + B_2X_2 + \dots + B_kX_k + B_0 \quad (2)$$

In the above equation, \hat{Y} is the predicted y-value, B is an unstandardized regression coefficient, k is the number of variables in the model, and B0 is the y-intercept (Cohen and Cohen, 2003). Therefore, in the initial models, \hat{Y} represents the measure of prescribing decisions (comfort level, refilling, and first-time prescribing), and in the fourth model, it would represent the measure of willingness to prescribe. The B-values are the unstandardized regression coefficients for each of the physician characteristics, patient variables, and package insert variables.

Independent variables were blocked together into three categories: physician characteristics, patient characteristics, and package insert excerpt characteristics, as described above in the measures section. The first block of predictors entered into the model was that of physician characteristics, which included year of initial licensure, gender, region of state, medical discipline, and estimated percentage of patients with a known history of substance abuse. The second block of independent variables for the model included the patient characteristics, which were type of pain and history of substance abuse. The third block of predictors was made up of the package insert variables. This was the final block of main effects in the models because it was the focus of the project and in hierarchical terms, its R^2 value indicates the amount of variance the package insert information provides over and above the other main effects. Strength of warning was either “strong” or “not strong,” a presence or absence of advice, and

presence or absence of definitions given in each excerpt. The interaction terms were added as fourth, fifth, and sixth blocks.

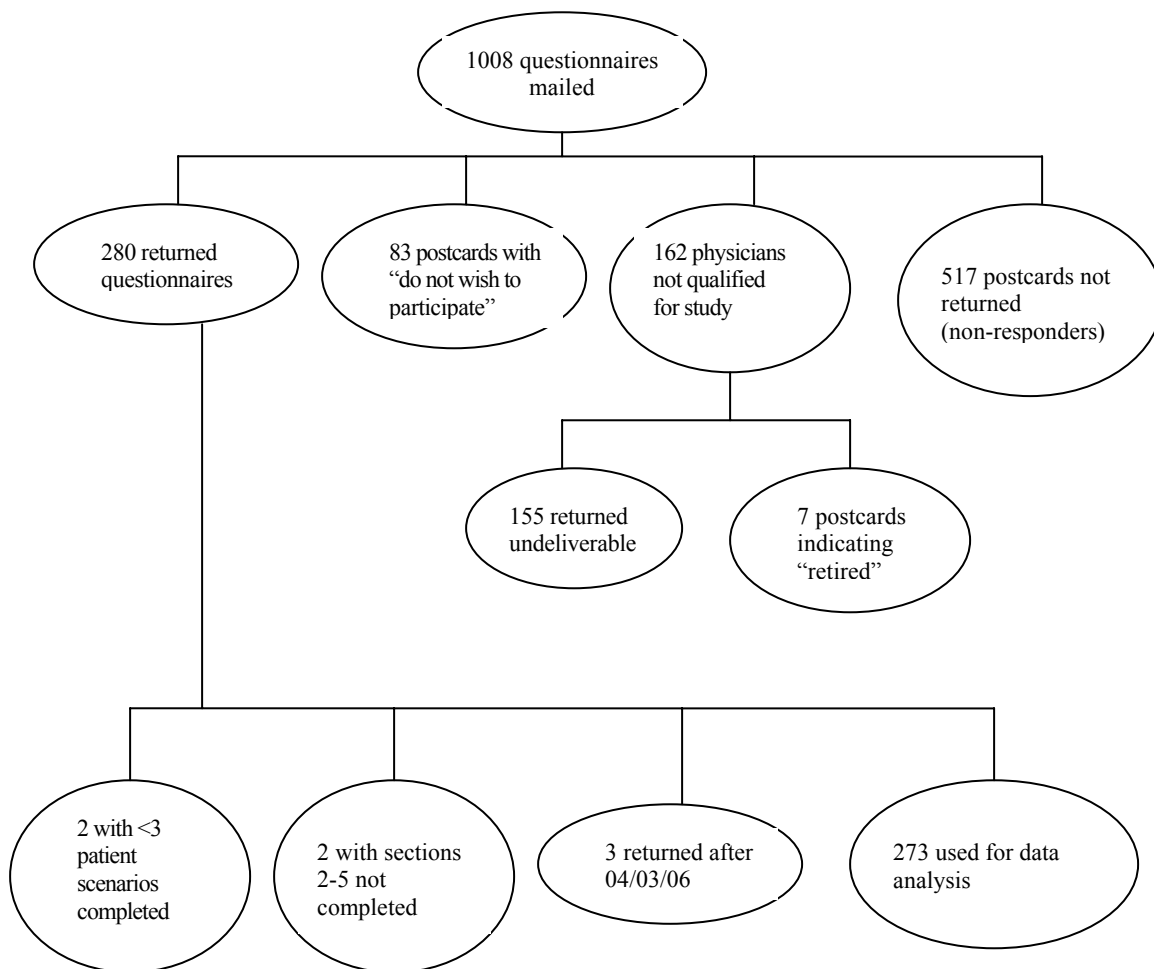
CHAPTER 5

Results

Response Rate

Of 1008 questionnaires mailed, 155 were returned undeliverable and 7 were returned stating “retired” on the postcard, leaving an actual sample size of 846. A total of 273 questionnaires met the criteria for a complete questionnaire and were used for analysis. Based on the sample size of deliverable questionnaires, the response rate was 32.3%. Eighty-three (9.8%) physicians returned the postcard with the box labeled “I do not wish to participate in this survey” checked. Interestingly, more questionnaires were returned than postcards. Although 277 questionnaires were returned before the cut-off date of April 3rd, 2006, only 246 postcards indicating the questionnaire had been completed were received. Figure 5.1 shows the numbers of questionnaires and postcards returned. The postcards were the only means of tracking responders and non-responders. Because more questionnaires than postcards were returned, some responders’ characteristics were accounted for as non-responders.

Figure 5.1 Flowchart of questionnaire responses



Responders and Non-Responders

Although responders were tracked to prevent mailing second questionnaires to responding physicians, postcards identifying the responders were separate from returned questionnaires, maintaining anonymity of responders. Characteristics of responders and non-responders were analyzed for significant differences on the variables of gender, region of practice, and initial year of licensure. Table 5.1 displays these characteristics. Chi-square analysis revealed no statistically significant differences between responders and non-responders with respect to gender or region of practice. Although year of licensure was a continuous variable, it was not normally distributed, dictating that a nonparametric test was more appropriate. The Mann-Whitney U-test revealed that responders had been practicing significantly longer than non-responders, with initial year of licensure having median values of 1985 and 1992, respectively. Initial year of licensure was also significant in the regression models, as discussed below. Although the impact of the significant difference between non-responders and responders is unknown, it would be expected that the data would shift toward increased prescribing, since this was the case among responders.

Table 5.1 Characteristics of responders and non-responders

Variable	Responders	Non-responders	p-value
<i>Gender(%)</i>			<i>0.070</i>
Male	74.4	66.1	
Female	23.1	28.1	
Unknown	2.5	5.8	
<i>Region of practice (%)</i>			<i>0.360</i>
Urban	65.9	67.2	
Southwestern	9.9	7.0	
Other non-urban	23.1	20.7	
Unknown	1.1	5.1	
<i>Year of licensure (median)</i>	1985	1992	<i><0.001</i>

Responding physicians reported a median estimate of 5% of patients they see having a known history of substance abuse, ranging from 0%-100%. The interquartile range was 2%-10%. The one physician that reported 100% was an addiction medicine specialist. One physician reporting 75% of patients with a known history of substance abuse participated in correctional facility work. This information was written in as a comment by the respondents. Other respondent comments can be found in Appendix J of this document.

Objective 1: Definitions of Addiction and Dependence

To gather information about physicians' impressions of the terms "addiction" and "drug dependence," physicians were provided with a list of characteristics and asked to check any features they felt were necessary for the condition in question to exist. These characteristics included: abuse, craving, drug-seeking behavior, physical dependence, psychological dependence, tolerance, and withdrawal. Table 5.2 shows the frequency

with which each was chosen. More physicians associated abuse, craving, drug-seeking behavior, psychological dependence, and withdrawal with addiction than with drug dependence, while more physicians felt that physical dependence and tolerance were necessary for drug dependence.

Table 5.2 Frequency of chosen factors necessary for addiction and drug dependence

Term	Drug dependence Frequency (%)	Addiction Frequency (%)
Abuse	89 (32.6)	210 (76.9)
Craving	121 (44.3)	236 (86.4)
Drug-seeking behavior	116 (42.5)	241 (88.3)
Physical dependence	207 (75.8)	187 (68.5)
Psychological dependence	198 (72.5)	217 (79.5)
Tolerance	175 (64.1)	169 (61.9)
Withdrawal	175 (64.1)	183 (67.0)

For the conditions of addiction and drug dependence, the terms physical dependence, psychological dependence, tolerance, and withdrawal were chosen as necessary by more than 50% of physicians. Abuse, craving, and drug-seeking behavior, however, were chosen by more than 50% of physicians for addiction but not for drug dependence.

Objective 2: Sources Used for Drug Information

Physicians were asked to rate the frequency with which they consult various sources for drug abuse and dependence information, and other drug information.

Frequency was defined as never (0), yearly (1), monthly (2), weekly (3), or daily (4).

shows the mean and median frequency for each source consulted for drug abuse and

dependence information and other drug information.

Table 5.3 Sources consulted by physicians

Source	Drug Abuse Info Mean (median)	Other Info Mean (Median)
Manufacturer	0.15 (0)	0.39 (0)
Drug Information Center	0.21 (0)	0.33 (0)
Internet	1.03 (0)	1.55 (2)
Package Insert	1.32 (1)	1.95 (2)
Personal Digital Assistant	0.98 (0)	1.54 (0)
Pharmacist	1.27 (1)	1.96 (2)
Physicians' Desk Reference	1.61 (1)	2.39 (3)
Other	0.40 (0)	0.49 (0)

As with the measure of factor importance, a mean was calculated for the consulted source even though the frequency is on an ordinal scale. The mean was used only for ranking purposes. For both drug abuse/dependence and other information, the Physicians' Desk Reference (PDR) was the most frequently used source. Pharmacists and package inserts were the next highest ranking for both types of information. Manufacturers and drug information centers ranked the least frequently used. For all sources consulted, the frequency was lower for drug abuse/dependence information than for other information, and the overall frequency of sources consulted was low. Most physicians who marked a frequency other than "never" for the "Other" category did not write in their other sources. Other sources reported by physicians listed in Table 5.4.

Table 5.4 List of “Other” sources consulted by physicians for drug information

- Poison Control Center
- Pharmacology textbook
- UpToDate online
- Primary literature
- “Drug reps”
- “Medical students – PDA by proxy?”
- “Unbiased sources”

Some of these sources could be classified in other categories: UpToDate could be classified as an internet source, and drug sales representatives could be classified as manufacturer contact.

Objective 3: Regression Models

Four regression models were evaluated. The dependent variables were all measures of physician prescribing decisions: comfort with the prior physician’s choice, likelihood of refilling the prescription, likelihood of prescribing if the respondent was the first physician to see the patient, and willingness to prescribe. Answers to three questions pertaining to prescribing decisions were on a 4-point Likert scale: not at all (0), not very (1), somewhat (2), or definitely (3). The dependent variable in the fourth model, “willingness to prescribe,” was created as a sum score from the first three variables, which were highly correlated with each other. Reliability testing for the scale resulted in a Crohbach’s alpha of 0.944. The correlation coefficients for comfort level with refill

likelihood and first prescription likelihood were 0.844 and 0.862, respectively. The correlation coefficient for refill likelihood and first prescription likelihood was 0.843.

For each model, the same six blocks of predictors were entered for hierarchical regression analysis. Table 5.5 summarizes the variables in the blocks of predictors entered into each model.

Table 5.5 Summary of variables entered into regression models

Block 1: Physician Characteristics

Gender

Initial year of licensure

Estimated percent of patients with a known history of substance abuse

Practice region (Southwestern, urban, other rural)

Medical discipline (emergency, family practice, internal medicine, other)

Block 2: Patient Characteristics

Type of pain being treated (acute, cancer, CNMK, CNMU)

History of substance abuse (none, past, current)

Block 3: Package Insert Characteristics

Strength of warning in package insert (strong, not strong)

Presence of direct advice in package insert (present, not present)

Presence of definitions in package insert (present, not present)

Block 4: Interaction terms for type of pain with history of substance abuse

Block 5: Interaction terms for type of pain with warning strength

Block 6: Interaction terms for history of substance abuse with warning strength

For nominal variables with more than 2 categories, indicator variables were created. For a physician's practice region, the reference group was Southwestern Virginia, and indicator variables were designated for urban and other rural. For medical discipline, emergency medicine (EM) was the reference group, with indicator variables created for family practice (FP), internal medicine (IM), and other. Type of pain was in reference to chronic, non-malignant pain of unknown etiology (CNMU) with indicator

variables for acute, cancer, and chronic, non-malignant pain of known etiology (CNMK).

For the history of substance abuse, the reference group was “none,” and indicator

variables were created for past history and current use.

All four models displayed overall significance at $p < 0.001$. For all four models, the blocks for physician, patient, and package insert characteristics, and interactions between pain and history of substance abuse were significant. The blocks for interactions between warning strength with type of pain and with history of substance abuse were not significant in any model. Table 5.6 shows the overall adjusted R^2 , R^2 change, and p -values representing the significance for each block of predictors for the four models.

Table 5.6 Statistics for predictor blocks for four initial regression models

	Comfort model ΔR^2 (p-value)	Refill model ΔR^2 (p-value)	1 st doctor model ΔR^2 (p-value)	Willingness model ΔR^2 (p-value)
Physician characteristics	0.036 (<0.001)	0.021 (0.006)	0.033 (<0.001)	0.032 (<0.001)
Patient characteristics	0.362 (<0.001)	0.377 (<0.001)	0.348 (<0.001)	0.339 (<0.001)
Package insert characteristics	0.031 (<0.001)	0.023 (<0.001)	0.032 (<0.001)	0.031 (<0.001)
Interactions: type of pain with history	0.018 (<0.001)	0.010 (0.009)	0.018 (<0.001)	0.016 (<0.001)
Interactions: type of pain with warning strength	0.002 (0.293)	0.002 (0.250)	0.001 (0.513)	0.002 (0.358)
Interactions: history with warning strength	0.001 (0.526)	0.003 (0.112)	0.000 (0.756)	0.001 (0.423)
Adjusted R^2	0.435	0.420	0.417	0.466

Because the predictor blocks for interactions between warning strength with type of pain and history of substance abuse were not significant, the individual regression coefficients were not further examined. Appendix K contains unstandardized regression coefficients, standard errors, and p-values for all of the predictors in significant blocks for the four models.

Within the block of physician characteristics, neither gender nor estimated percentage of patients with a history of substance abuse was significant in any model. Initial year of licensure and medical discipline were significant for all four models. History of substance abuse and type of pain being treated were significant in the patient characteristics blocks for each model. Warning strength and the presence of definitions were both significant in all four models. The presence of advice in the package insert was significant for all but the refill model. Further exploration of the models follows.

Model 1: Comfort Level of Prior Prescription

For the first model, the dependent variable of physician prescribing decisions was measured by the question “How comfortable are you with the prior physician’s choice of medication for this patient?” The overall adjusted R^2 indicates that 43.5% of the variance in the level of comfort with a prior physician’s choice is explained by the physician, patient, package insert, and interaction terms entered into the initial model. Because the blocks for interaction terms for warning strength with type of pain and substance abuse were not significant, they were not included in the final model. The final model, then,

consisted of all predictors in the first four blocks described above. Based on the unstandardized regression coefficients, the equation for the final model is:

$$\begin{aligned} \text{Comfort level} = & \\ & -0.093(\text{gen}) + 0.11(\text{yr}) + 0.091(\text{urb}) + 0.166(\text{rural}) - 0.335(\text{FP}) - 0.342(\text{IM}) - 0.306(\text{other}) \\ & + 1.125(\text{acute}) + 1.437(\text{cancer}) + 0.243(\text{CNMK}) - 0.442(\text{past}) - 0.500(\text{curr}) - 0.270(\text{str}) - \\ & 0.169(\text{adv}) - 0.196(\text{def}) - 0.355(\text{ac*past}) + 0.198(\text{ac*curr}) + 0.414(\text{can*past}) \\ & + 0.364(\text{can*curr}) + 0.313(\text{CNMK*past}) + 0.086(\text{CNMK*curr}) - 21.069 \end{aligned}$$

(5.1)

Abbreviations used in the above equation are listed in Table 5.7. Estimated percent of patients with a known history of substance abuse was not included in the equation because the regression coefficient was 0.000.

Table 5.7 Abbreviations used in regression equation 5.1

- Gen = physician gender
- §Yr = initial year of physician licensure
- Urb = urban region of practice
- Rural = other rural practice region
- §FP = family practice specialty
- §IM = internal medicine specialty
- §Other = other medical discipline
- §Acute = acute pain
- §Cancer = cancer pain
- CNMK = chronic, non-malignant pain of known etiology
- §Past = past history of substance abuse
- §Curr = current history of substance abuse
- §Str = warning strength in package insert
- §Adv = advice in package insert
- §Def = definitions in package insert
- Ac*past = acute pain with a past history of substance abuse
- Ac*curr = acute pain with current recreational substance use

Table 5.7 Abbreviations used in regression equation 5.1 (continued)

- §Can*past = cancer pain with a past history of substance abuse
- §Can*curr = cancer pain with current recreational substance use
- CNMK*past = CNMK with a past history of substance abuse
- CNMK*curr = CNMK with current recreational substance use

§ significant at $p < 0.05$

The physician characteristics explain 3.6%, and patient characteristics explain 36.2% over and above the physician characteristics, based on the change in R^2 . The package insert characteristics of warning strength, advice, and definitions, then, explain an additional 3.1%, while the interactions between pain type and substance abuse history add an additional 1.8% to the model. The p-values for the change in R^2 were all < 0.001 .

Physicians who have been more recently licensed are more comfortable with a prior physician's choice. Acute and cancer pain significantly increased comfort level when compared to chronic, non-malignant pain of unknown etiology (CNMU). Chronic, non-malignant pain of known etiology (CNMK) did not significantly affect comfort level when compared to CNMU. Past or current history of substance abuse decreased comfort level compared to patients having no history of substance abuse. Strong warnings, the presence of advice, and the presence of definitions in the package insert excerpts decreased physician comfort level with the prior physician's choice of medication.

The reference groups for pain type and substance abuse history were CNMU and no history of substance abuse. Two interaction terms were significant in the initial model and were entered into the final model. The term for cancer pain and current history of substance abuse became non-significant in the final model; however, the interaction product for cancer pain and past history of substance abuse remained significant. This

indicated that the importance of the patient's history of substance abuse was dependent on the type of pain being treated. In this model, cancer pain, regardless of history of substance abuse, increases physicians' comfort level when compared to a patient with CNMU with no history of substance abuse. In other words, even though past and current history of substance abuse decrease comfort level, this becomes less important if the patient is experiencing cancer pain.

Model 2: Likelihood of Refilling

The second measure of physician prescribing decisions asked the question "How likely are you to refill this prescription?" The initial model (i.e. with all six blocks of predictors) for this question showed an overall adjusted R² of 0.418, and the final model had an adjusted R² of 0.416. Physician characteristics explain just 2.1% in this model, with patient characteristics adding 37.7%. Package insert characteristics contribute an additional 2.3% over and above physician and patient characteristics. Interactions between pain type and substance abuse history, while statistically significant, add another 1.0% of explanation of variance in frequency of refilling.

The resulting equation for the final model is depicted in equation 5.2.

$$\begin{aligned}
 & \text{Likelihood of refilling the prescription} = \\
 & 0.040(\text{gen}) + 0.011(\text{yr}) - 0.002(\%) + 0.104(\text{urb}) + 0.147(\text{rural}) - 0.177(\text{FP}) - \\
 & 0.161(\text{IM}) - 0.193(\text{other}) + 0.901(\text{acute}) + 1.585(\text{cancer}) + 0.290(\text{CNMK}) - \\
 & 0.281(\text{past}) - 0.374(\text{curr}) - 0.252(\text{str}) - 0.103(\text{adv}) - 0.153(\text{def}) - \\
 & 0.491(\text{ac}*\text{past}) - 0.113(\text{ac}*\text{curr}) + 0.244(\text{can}*\text{past}) + 0.176(\text{can}*\text{curr}) \\
 & + 0.113(\text{CNMK}*\text{past}) + 0.001(\text{CNMK}*\text{curr}) - 21.392
 \end{aligned}
 \tag{5.2}$$

Table 5.8 lists the abbreviations used in equation 5.2 and indicates which regression coefficients were significant.

Table 5.8 Abbreviations used in regression equation 5.2

- Gen = physician gender
- §Yr = initial year of physician licensure
- % = estimated percent of patients with known substance abuse history
- Urb = urban region of practice
- Rural = other rural practice region
- §FP = family practice specialty
- §IM = internal medicine specialty
- Other = other medical discipline
- §Acute = acute pain
- §Cancer = cancer pain
- §CNMK = chronic, non-malignant pain of known etiology
- §Past = past history of substance abuse
- §Curr = current history of substance abuse
- §Str = warning strength in package insert
- Adv = advice in package insert
- §Def = definitions in package insert
- §Ac*past = acute pain with a past history of substance abuse
- Ac*curr = acute pain with current recreational substance use
- Can*past = cancer pain with a past history of substance abuse
- Can*curr = cancer pain with current recreational substance use
- CNMK*past = CNMK with a past history of substance abuse
- CNMK*curr = CNMK with current recreational substance use

§ significant at $p < 0.05$

Reference groups for those predictors with indicator variables remained the same as in the first model. For pain, CNMU was the reference group, for physician specialty, emergency medicine, and for history of substance abuse history, “no history” was used.

As in the first model (comfort model), more recent licensure indicates that a physician is more likely to refill the prescription presented in the case scenario. Family

practitioners and internists are less likely to refill compared to emergency physicians. Not surprisingly, both acute and cancer pain increase likelihood of the physician refilling the prescription. CNMK was also significant in this model ($p=0.029$) but not for any other model. Past and current substance abuse histories again prove to have a negative effect on physician prescribing, as do strong package insert warnings and presence of definitions. The interaction for acute pain with a past history of substance abuse in this model was also significant, again suggesting that the importance of substance abuse history depends on the type of pain being treated. In this model, the interaction suggests that physicians are less likely to refill a prescription for acute pain if someone has a past history of substance abuse than they are for a patient with CNMU and no history.

Model 3: Likelihood of First Time Prescribing

The third measure of physician prescribing decisions was based on the question “how likely would you be to prescribe this medication if you were the first physician to see this patient?” In this model, the adjusted R^2 indicated that 41.8% of the variance in first prescribing could be attributed to the variables in the final model. Again, various aspects of physician, patient, and package insert characteristics proved to be important, as did interaction terms for pain type and substance abuse history. The final model is represented in equation 5.3. Table 5.9 defines abbreviations used and indicates statistically significant variables.

$$\begin{aligned}
& \text{First prescribing likelihood} = \\
& -0.081(\text{gen}) + 0.012(\text{yr}) + 0.002(\%) + 0.132(\text{urb}) + 0.231(\text{rural}) - 0.181(\text{FP}) - \\
& 0.239(\text{IM}) - 0.205(\text{other}) + 1.143(\text{acute}) + 1.389(\text{cancer}) + 0.181(\text{CNMK}) - \\
& 0.370(\text{past}) - 0.395(\text{curr}) - 0.276(\text{str}) - 0.175(\text{adv}) - 0.175(\text{def}) - 0.507(\text{ac*past}) - \\
& 0.051(\text{ac*curr}) + 0.376(\text{can*past}) + 0.273(\text{can*curr}) + 0.244(\text{CNMK*past}) - \\
& 0.019(\text{CNMK*curr}) - 21.623
\end{aligned}
\tag{5.3}$$

Table 5.9 Abbreviations used in regression equation 5.3

- Gen = physician gender
 - [§]Yr = initial year of physician licensure
 - % = estimated percent of patients with known substance abuse history
 - Urb = urban region of practice
 - [§]Rural = other rural practice region
 - [§]FP = family practice specialty
 - [§]IM = internal medicine specialty
 - Other = other medical discipline
 - [§]Acute = acute pain
 - [§]Cancer = cancer pain
 - CNMK = chronic, non-malignant pain of known etiology
 - [§]Past = past history of substance abuse
 - [§]Curr = current history of substance abuse
 - [§]Str = warning strength in package insert
 - Adv = advice in package insert
 - [§]Def = definitions in package insert
 - [§]Ac*past = acute pain with a past history of substance abuse
 - Ac*curr = acute pain with current recreational substance use
 - [§]Can*past = cancer pain with a past history of substance abuse
 - Can*curr = cancer pain with current recreational substance use
 - CNMK*past = CNMK with a past history of substance abuse
 - CNMK*curr = CNMK with current recreational substance use
- [§] significant at p<0.05

As in the first two models, more recent year of licensure is significant. The interpretation for this model is that more recently licensed physicians would be more likely to prescribe the drug if they were the first to see the patient presented in the case

scenario than would physicians who have been practicing for a longer period of time. In this model only, region had an impact. The reference group for region was Southwestern Virginia. The interpretation of this regression coefficient would be that compared to physicians in Southwestern Virginia, physicians in other rural areas are more likely to prescribe the drug as the first physician seeing the patient. Family practice and internal medicine specialties had a negative impact when compared with emergency physicians, as did either current substance abuse or a past history of substance abuse. Again, the presence of acute or cancer pain increased the likelihood of prescribing, and strong warnings, presence of advice, and definitions in package insert information decreased potential prescribing. As in the first two models, likelihood of prescribing is also dependent on the interaction between type of pain and substance abuse history, and the impact of substance abuse history on prescribing is dependent on the type of pain being treated. Here, a past history of substance abuse has a negative impact if the pain type is acute, but a positive impact if the patient is experiencing cancer pain as compared to a patient with no substance abuse history and CNMU.

Model 4: Willingness to Prescribe

All three previous dependent variables gauge a physician's willingness to prescribe a drug for the case scenario presented. In this final model, physician prescribing decisions were measured as a sum scale of the dependent variables in the first three models. That is, a physician's answers to the first three questions were added together to create a "willingness score." This was done after correlation and reliability

testing indicated that the three prior measures were highly correlated with one another. Correlation coefficients were all >0.80, and Cronbach's alpha, a measure of reliability, was 0.944. A higher score on the scale translated to being more willing to prescribe the drug. The adjusted R² for the final model indicated that 46.6% of the variance in willingness to prescribe could be explained by the variables in the model. This composite dependent variable model explained between 3.1% and 4.9% more variance in physician prescribing than any of the individual dependent variables alone.

Equation 5.4 represents the regression model for willingness to prescribe, and Table 5.10 shows abbreviations used in the equation and indicates significant variables.

$$\begin{aligned}
 & \text{Willingness to prescribe=} \\
 & -0.134(\text{gen}) + 0.034(\text{yr}) + 0.327(\text{urb}) + 0.546(\text{rural}) - 0.693(\text{FP}) - 0.742(\text{IM}) - \\
 & 0.710(\text{other}) + 3.170(\text{acute}) + 4.411(\text{cancer}) + 0.713(\text{CNMK}) - 1.075(\text{past}) - \\
 & 1.269(\text{curr}) - 0.797(\text{str}) - 0.448(\text{adv}) - 0.524(\text{def}) - 1.298(\text{ac*past}) + 0.025(\text{ac*curr}) \\
 & + 1.034(\text{can*past}) + 0.816(\text{can*curr}) + 0.670(\text{CNMK*past}) \\
 & + 0.067(\text{CNMK*curr}) - 64.092
 \end{aligned}
 \tag{5.4}$$

Table 5.10 Abbreviations used in equation 5.4

- Gen = physician gender
- §Yr = initial year of physician licensure
- % = estimated percent of patients with known substance abuse history
- Urb = urban region of practice
- Rural = other rural practice region
- §FP = family practice specialty
- §IM = internal medicine specialty
- §Other = other medical discipline
- §Acute = acute pain
- §Cancer = cancer pain
- CNMK = chronic, non-malignant pain of known etiology
- §Past = past history of substance abuse
- §Curr = current history of substance abuse
- §Str = warning strength in package insert

Table 5.10 Abbreviations used in equation 5.4 (continued)

- §Adv = advice in package insert
 - §Def = definitions in package insert
 - §Ac*past = acute pain with a past history of substance abuse
 - Ac*curr = acute pain with current recreational substance use
 - §Can*past = cancer pain with a past history of substance abuse
 - Can*curr = cancer pain with current recreational substance use
 - CNMK*past = CNMK with a past history of substance abuse
 - CNMK*curr = CNMK with current recreational substance use
- § significant at $p < 0.05$

Results were similar to those of the other models. Significant positive predictors of willingness to prescribe were initial licensure year and acute or cancer pain.

Significant negative predictors were medical discipline other than emergency medicine, past substance abuse history or current substance abuse, strong package insert warnings, and advice or definitions in package inserts. The interaction terms again indicated that willingness to prescribe for someone with a history of substance abuse depended on the type of pain being treated.

Usefulness of Package Insert Information

Physicians were asked to rate how useful they found the package insert information provided in making a clinical decision for the patient. The same previously described 4-point Likert scale ranging from “not at all” to “definitely” was used.

Physician ratings were collapsed into two categories as follows: not at all and not very were collapsed into a category called “not useful,” while somewhat and definitely were

collapsed into a “useful” category. Chi-square for physician-rated usefulness and the presence of advice was performed and revealed a significant difference ($\chi^2=11.43$, $p<0.001$).

Table 5.11 shows the frequencies of physician-rated usefulness for the presence or absence of advice provided in the package insert.

Table 5.11 Contingency table for physician-rated usefulness and advice

	Not useful	Useful
No advice	173	344
Advice present	136	427

Overall, more physicians rated package inserts as useful; however, the largest number of package inserts rated as useful were those with advice present. The lowest number in the contingency table is the frequency of physicians rating a package insert with advice as not useful. More physicians rated package inserts as not useful when there was no advice given than when advice was given; however, even when no advice was present in the package insert, more physicians rated it useful than not useful.

Assessment of Instrument

Although warning strength for each package insert excerpt was determined a priori, physicians were also asked to rate the warning strength by choosing the Controlled Substance Act (CSA) schedule that they felt was most appropriate for the medication

associated with the package insert excerpt provided. Responses were collapsed into two schedule categories: schedule II and other. Warnings determined as “strong” by the researchers should correspond with physicians choosing the highest control level, or CII. Table 5.12 shows the frequencies of schedule choice and pre-assigned warning strength.

Table 5.12 Contingency table for researcher and physician-rated warning strength

	Schedule II	Other
Strong	364	177
Not strong	147	389

Chi-square analysis revealed that the frequencies in each cell of the contingency table were not the same ($X^2=171.54$, $p<0.001$). Examination of the contingency table frequencies suggests that researchers’ and physicians’ ratings agreed.

A second assessment of the instrument examined regression coefficients with ranking of factor importance. Physicians were overtly asked to rate the importance of factors in their clinical decision making. If factors were rated as important by physicians, then the rankings of the importance of the factors should correspond with the rankings of the regression coefficients for the variables.

Table 5.13 shows the mean response for the six factors and the regression coefficients for the corresponding variables in the final regression models. It is important to note that while the scale on which the physicians rated the factors was ordinal, a mean

was calculated because it was being used only for the purpose of ranking the order of physician-rated importance of these variables.

Table 5.13 Physician-rated importance of factors in clinical decision making and corresponding regression coefficients

Factor in package insert	Mean Physician Rating	Regression Coefficients			
		Comfort	Refill	1 st Doctor	Scale
Type of pain being treated (cancer, acute)	2.85	1.279	1.727	1.445	4.433
Patient's history of substance abuse (current and past)	2.79	0.891	0.882	1.018	2.779
Warning strength	1.93	-0.442	-0.390	-0.376	-1.124
Advice present	1.86	-0.426	-0.201	-0.251	-0.717
Definitions present	1.28	-0.296	-0.274	-0.299	-0.850
		-0.173	-0.103	-0.169	-0.446
		-0.181	-0.145	-0.166	-0.487

Generally, the physician ranking of factor importance corresponded with the ranking of the corresponding regression coefficient, with the exception of advice and definitions present. Note that it is the magnitude of the regression coefficient that was taken into account because the sign indicated only the direction of the relationship to the dependent variable. Based on both physician rating and regression coefficients, the type of pain being treated was clearly the most important factor, and warning strength was always higher than either advice or definitions present. With respect to history of substance abuse, at least one regression coefficient ranked higher than warning strength in all cases.

CHAPTER 6

Discussion and Conclusions

Study Summary

This survey study was designed to elucidate several issues surrounding drug abuse and dependence and physician prescribing behaviors, particularly as they relate to information provided in package inserts. A total of 1,008 physicians practicing in the Commonwealth of Virginia in general medical disciplines were mailed a questionnaire packet. Several contacts were employed to increase responses, resulting in an achieved response rate of 33.1%. Items on the questionnaire addressed physician prescribing decisions, impressions of package insert information, ideas about addiction and drug dependence, sources consulted for drug information, and demographics.

Research Objectives and Results

Objective 1: Definitions of Addiction and Drug Dependence

One of the objectives of this study was to describe how currently practicing physicians view the terms “addiction” and “drug dependence.” Physicians more frequently associated physical dependence and tolerance with “drug dependence” than with “addiction,” suggesting that physicians tend to view drug dependence as a physiological state rather than the substance use disorder described in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Abuse, craving, drug-seeking behavior,

psychological dependence, and withdrawal were more frequently associated with addiction than with drug dependence. This points to physicians viewing addiction as the disease state of Drug Abuse or Drug Dependence as described in the DSM. This disparity surrounding these terms can be confusing when reading package inserts that do not further explain what is intended by “drug dependence” or simply “dependence.” Because no specific statistical tests have been used to explore these data, the significance of these apparent differences in physicians’ ideas about these terms remains unknown. However, it is evident that many physicians do not appear to view the terms addiction and drug dependence equally.

Objective 2: Sources of Drug Information

A second objective of this study was to describe sources that physicians refer to for drug information. Results showed that the three most consulted sources were the Physicians’ Desk Reference (PDR), package inserts, and pharmacists. It is important to note that the PDR is in fact a collection of package inserts. This being said, it appears that package inserts are an essential source of information for physicians, making standardized terminology imperative for providing information to prescribers. Pharmacists, another source of information for physicians, may also turn to the package insert for drug information, although this has not been explored in the current study.

Overall, the frequencies with which physicians report consulting sources is low, with median values for most sources translating to “never” or “yearly.” This begs the

question as to why physicians are not consulting drug information sources, particularly at a time when there are so many medications from which to choose?

Objective 3: Regression Models

Four regression models were used to examine physician prescribing decisions. These models were: comfort with a prior physician's choice, willingness to refill the prescription, likelihood of prescribing as the first physician seeing the patient, and a sum score of the first three measures. In all four regression models, the three blocks of main effects predictors were significant, as was the added predictor block of an interaction between type of pain and substance abuse history. Two other blocks of interaction terms, one for warning strength with pain type and one for warning strength with substance abuse history, were not statistically significant.

Initial year of licensure for physicians was consistently significant in all four models and indicated that more recent year of licensure had a positive impact on prescribing. That is, physicians who were more recently licensed tended to be more comfortable with a prior physician's choice, more likely to refill the prescription, and more likely to prescribe the drug if initially seeing the patient. This was also reflected in the fourth model which showed that physicians who have been more recently licensed were more willing to prescribe the drug overall. This could be attributed to their more recent education on pain management issues, or could be a reflection of deeper suspicion or concern about substance abuse and dependence by physicians who have had more years of experience.

Physician specialty was also found to be significant in all four models. With respect to emergency physicians, family practice and internists were less likely to be comfortable with a prior physician's choice, refill the medication, or to prescribe the medication as the first physician. This was also demonstrated in the overall willingness model. Emergency physicians may make decisions differently for several reasons. First, they do not see the same patients on a regular basis. While there are those who tend to use emergency rooms as primary care because of insurance issues, this is the exception and not the rule for most individuals. Emergency physicians, then, do not tend to have an ongoing relationship with their patients. The effect of this on prescribing decisions is unknown and was not explored in this study. Additionally, emergency patients are frequently discharged with instructions to follow-up with their regular physicians. In other words, the emergency physician takes care of the immediate issue, but it is the patient's regular physician who continues to monitor the patient and maintain or change drug therapy. The long-term monitoring that a primary care physician performs could also explain differences in prescribing decisions between emergency physicians and other general practitioners. The designation of "other" did not have significant impact in either the refill or first physician models.

Region of practice was significant in only one initial model, and became insignificant once entered in to the final model. It was thought that the problems with Oxycontin® in Southwestern Virginia in recent years may cause physicians in that region to make different decisions than those in urban areas or other rural areas of the

Commonwealth. However, this proved to have almost no impact for the purposes of this project.

Patient characteristics were clearly the most important block of predictors in these models. For all four models, this block of predictors contributed the most to explaining the variance. Physicians were more likely to prescribe for acute and cancer pain when compared to CNMU in all four models; however, CNMK was not significantly different from CNMU. In this survey, CNMK was presented as severe osteoarthritis unresponsive to acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). It is possible that if a different diagnosis had been used, that CNMK may have played a larger role. Different diagnoses of CNMK were not addressed in this study but could be important.

A patient's history of substance abuse was also clearly important to physicians when making clinical decisions about prescribing analgesics. Patients with a history of substance abuse and those who currently use drugs recreationally might raise caution and decrease a physician's willingness to prescribe or refill a prescription for a controlled substance, with respect to patients with no history of substance abuse. However, this became less important when treating acute or cancer pain as opposed to CNMU, as demonstrated by the significant interactions found in the models.

The variability in package insert information about drug abuse and dependence was a main focus of this study. Variability was measured with three variables: strength of the warning about drug abuse and dependence, the presence of advice in the package insert, and definitions of terms used in the insert. This block of predictors was significant in all four models. Table 6.1 Physician-rated importance of factors in clinical decision

making and corresponding regression coefficients illustrates the amount of variance in each model explained by package insert variability over and above physician and patient characteristics.

Table 6.1 Physician-rated importance of factors in clinical decision making and corresponding regression coefficients

	R² change	Significance
Comfort	0.031	<0.001
Refill	0.023	<0.001
First physician	0.032	<0.001
Willingness scale	0.031	<0.001

Between 2.3% and 3.1% of the variance in physician prescribing decisions could be explained by the variability in the package insert. All three predictors were significant in all models, except that the presence of advice did not have a significant effect on physicians' decisions to refill a prescription. The finding that the PDR and package insert were ranked among the top three sources consulted for drug abuse and dependence information suggests that package insert information on drug abuse and dependence was important to physicians. This further underscores the need for standardization of definitions of terms surrounding the issue of drug abuse and dependence and the need for more useful information such as clinical advice to be included in package inserts.

Limitations of Study

Because the sampling frame for this study was limited to the Commonwealth of Virginia, the results may not be generalizable to a population of United States

physicians. While the Commonwealth of Virginia does have urban, suburban, and rural regions, and has areas that have had drug abuse issues, it is difficult to say how closely Virginia physicians' responses would represent those from other states without including physicians from other areas.

It is unknown whether or not physicians' responses to questionnaire items about prescribing decisions reflect what they would actually do in clinical practice. Many variables that may affect physicians' prescribing decisions, such as the patient's gender, age, ethnicity, and socioeconomic status, were held constant in this survey because they were not the focus of this study. Additionally, many other details present in a clinical setting were left out in the interest of creating more concise scenarios. These include lab results and further details about prior treatment received. Furthermore, a physician cannot interact with nor observe behaviors of patients presented on a paper questionnaire. All of these variables may affect decisions that physicians make about prescribing.

The patients in the case scenarios in this study were all 38 year old Caucasian males. Variables of patient age, race/ethnicity, and gender were kept constant because they were not the focus of this study and to maintain a reasonable number of variables examined. It is possible that these variables contribute to a physician's decision to prescribe opioids for pain, and keeping them constant could have decreased the variance explained by the models presented here. However, it was felt defining the patient variables was a better option than leaving them unknown and allowing each physician to make different assumptions about patient characteristics.

Physicians are often considered to be low responders in survey research. In this survey, a response rate of 32.3% was achieved. While this seems to be low, several of the articles reviewed surveyed physicians in a narrower sampling frame. These included a single medical school (Brown et al., 1997), members of a professional organization representing only one medical discipline (Greenwald et al., 1999), a small collaborative research network (Potter et al., 2001), and a single metropolitan area (Davies et al., 1997). People are more likely to respond to a survey that is of interest to them and is being conducted by a group to which they feel some sense of loyalty. Therefore, narrowing a sampling frame may increase response rate; however, generalizability of results is sacrificed. With regard to sample size, the database from which the information was drawn was not as up to date or accurate as believed, and decreased the reachable sample size from 1008 to 846.

A large national study of physicians from various medical specialties obtained a response rate of 27.46% (Turk et al., 1994). While this study had a lower response rate, the sample size and sampling frame allowed the results to be generalized to a larger population, assuming that non-response error was not higher than in the other studies. Regarding this study, those holding MD and DO degrees are certainly not the only professionals with prescribing power. This sampling frame excludes residents and interns and those with limited prescribing power such as dentists, nurse practitioners, and physicians' assistants. These professions were excluded as they do not have full autonomy in decision-making and therefore may not be able to answer some of the items on the questionnaire. As previously mentioned, this survey sampled physicians in the

Commonwealth of Virginia only, so those practitioners who are licensed or residing outside of Virginia are not included in the sample. Thus, the results of this study could not be easily generalized to all physicians in the United States. This project would, however, serve as a springboard for a larger, national sample in the future.

There may be some non-response error in that physicians who responded had an earlier year of licensure than did non-responders. The impact of this on the results is unknown, but year of licensure was a significant predictor in all four models. Based on the results of the responders and the difference in licensure year between responders and non-responders, the models would err on the side of less prescribing.

With respect to other physician characteristics, there was no difference between responders for region or gender. Region for non-responders was determined by the researcher based on the ZIP code, but was subjectively reported by responders. It is possible that the responding physicians view themselves as being in a different region than the researcher would assign based on ZIP code. Names of non-responding physicians were evaluated for likely gender by the researcher. Any names that were gender neutral or foreign names that could not be assigned a gender were considered unknown. It is possible that some non-responders were assigned to the incorrect gender category. Based on the responses for medical discipline, it is apparent that board certification does not always reflect a physician's self-reported specialty. Medical discipline for responders and non-responders was not evaluated.

Finally, it is possible that some items on the questionnaire were not measuring what the researchers intended, or were interpreted differently by respondents.

Specifically, three physicians made comments that indicate the item about classifying the medication into a CSA schedule was misread as classifying which level of drug control should be prescribed for the patient. It is possible that other physicians also misread this item; however, the chi-square analysis performed relating warning strength to physician-rated schedule indicates that this was not the case.

The limitations of this study are only minor weaknesses. Sufficient power was achieved in the study as evidenced by the significant findings in the regression models and other statistical analyses performed.

Areas for Future Research

The final objective of this dissertation was to provide groundwork for future research. This project contributes to the literature about factors affecting physicians' prescribing decisions by demonstrating that information presented about medications can affect their decision-making process. Surveys of larger size and broader sampling frame could support or refute the results found in this study.

Three areas of variability in package insert information concerning drug abuse and dependence have been identified as significantly affecting the physician's perceptions of the medication. All three were measured only as nominal variables, however, and further research into more specific aspects of warning strength, advice given, and definitions relating to terms used in package inserts is warranted. Physicians are not the only health care providers who consult package inserts for drug information.

Research about how information is communicated to other health care professionals such as nurses and pharmacists would also prove interesting.

During the course of the completion of this project, the Food and Drug Administration (FDA) released statements on changes to the format of package inserts for medications. Research on current package inserts can help to guide regulators in forming new guidelines for updated package insert content. These new package inserts will then need to be evaluated.

Conclusions

Many factors were identified as having an affect on physicians' prescribing decisions. These include physician characteristics such as year of licensure and medical discipline, patient characteristics relating to type of pain and substance abuse history, and package insert information provided to physicians. The three areas of package insert variability identified in this study were the strength of the warning about substance abuse and dependence, the presence of clinical advice given, and the presence of definitions of terms used in the package insert.

The terms "addiction" and "drug dependence" were generally not viewed as interchangeable by physicians. Drug dependence was more associated with a physiological state and addiction with a psychological state. Sources consulted by physicians were varied, with the top three reported as the PDR, package inserts, and pharmacists. This was true for both drug abuse/dependence information and for other drug information. Physicians rated package inserts offering direct advice as more useful

than those without any advice. Advice presented in package inserts was related to patient counseling, prescribing to substance abusers, and how to treat withdrawal.

Overall, the two studies performed show that: 1) there is high variability in drug abuse and dependence information in package inserts, 2) the package insert continues to be an important source of drug information for physicians, and 3) package insert information can affect a physician's prescribing decisions. This could affect the quality and safety of patient care. As the FDA revises the requirements for product labeling for new medications, continued evaluation of the package inserts for clarity and consistency is imperative.

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APPENDIX A**Complete list of package inserts included in Preliminary Study**

Generic Name	# Entries in database
Alprazolam	1
Amphetamine	1
Buprenorphine	1
Butalbital	2
Butorphanol	1
Caffeine	3
Chlorazepate	1
Clonazepam	1
Codeine	3
Dexmethylphenidate	1
Dextroamphetamine	3
Diazepam	1
Estazolam	1
Fentanyl	2
Hydrocodone	10
Hydromorphone	1
Hydroxyzine	2
Mepiridine	1
Methamphetamine	1
Methylphenidate	3
Modafinil	1
Morphine	6
Nalbuphine	1
Oxycodone	7
Oxymorphone	1
Pemoline	1

Pentazocine	2
Pentobarbital	1
Phendimetrazine	1
Phenobarbital	2
Phentermine	2
Promethazine	1
Propoxyphene	2
Sodium Oxybate (GHB)	1
Tramadol	2
Zaleplon	1
Zolpidem	1

APPENDIX B

Qualitative codes and meanings for Preliminary Study

Code	Meaning
AEAb	Abuse is listed in the adverse effects section of the package insert
AEAd	Addiction is listed in the adverse effects section of the package insert
AEPsD	Psychological dependence is listed in the adverse effects section of the package insert
AEWD	Withdrawal is listed in the adverse effects section of the package insert
AntW	The package insert contains a warning about administering an antagonist
CompAbP	The abuse potential of the drug is compared to that of a known drug of abuse
CompDep	The dependence potential of the drug is compared to that of a known drug of abuse
CompNot	The package insert states that the drug is NOT like a particular drug of abuse
CompPhD	The physical dependence of the drug is compared to that of a known drug of abuse
CompPsD	The psychological dependence of the drug is compared to that of a known drug of abuse
CompSP	The chemical structure and pharmacology of the drug are compared with a known drug of abuse or a class of drugs with abuse potential
DTol	The word “tolerance” is discussed, described, or defined
D/C	The package insert contains a warning against abrupt discontinuation of the drug
DChrInt	The package insert discusses, describes, or defines chronic intoxication
DIDOA	The package insert discusses drug interactions of the drug with other drugs of abuse
DIDOAN	There is no discussion of interactions between the drug and other drugs of abuse
DifAbAd/PhDT	There is a statement that abuse zdbgbg
DifTolPhD/PsD	There is a statement that tolerance and physical dependence are different from psychological dependence
DInWD	Withdrawal symptoms in infants are described
Disc +	The drug was discriminated as being similar to another drug of abuse
DiscHu –	The drug was not discriminated by humans as being similar to a known drug of abuse

DiscHu +	The drug was discriminated by humans as being similar to a known drug of abuse
DphD	Physical dependence is discussed, described, or defined
DPsD	Psychological dependence is discussed, described, or defined
DWD	Withdrawal is discussed, described, or defined
DWDdog	The package insert indicated that a withdrawal syndrome was found in dogs upon discontinuation of the drug
EqAddDDPsD	Addiction, drug dependence, and psychological dependence were equated with each other
EqPsyDAd	Psychological dependence was equated with addiction
ExtUseW	There is a warning against extended use of the product
HospEDrpt	The package insert discussed Emergency room hospital visits associated with the use of the drug
HowAb+W	The package insert describes or discusses how the drug is abused
HxDACa	The package insert indicates that the drug should be used with caution in patients with a history of drug abuse
HxDACI	The package insert states that the use of the drug is contraindicated in patients with a history of drug abuse
HxDAW	The package insert indicates that the drug should not be used in patients with a history of drug abuse
Limit	The package insert gives a dose limit or time limit for the use of the drug
MBHF	The package insert contains the phrase “May be habit forming”
NDInWD	The package insert states that infants born from mothers using the drug experience withdrawal, but symptoms are not described
NDPhD	The term “physical dependence” is used in the package insert, but is not otherwise described or defined
NDPsD	The term “psychological dependence is used in the package insert, but is not otherwise described or defined.
NDTol	The term “tolerance” is used in the package insert, but is not otherwise described or defined
NDWD	The term “withdrawal” is used in the package insert, but is not otherwise described or defined
None	The package insert contains no information on drug abuse or dependence potential
NTPW	There is a warning against the use of the drug or certain dosage forms of the drug in non-tolerant patients
OnOffse+	The package insert states that the onset and offset of the drug indicate that it has increased potential for abuse
PdD+rab	Physical dependence has been seen in dogs and rabbits
PhD+dog	The package insert states that physical dependence occurred in dogs
PID/C	Patient information in the package insert contains a warning against abrupt discontinuation of the drug

PIDDD	Patient information in the package insert discusses, describes, or defines “drug dependence”
PIDTol	Patient information in the package insert discusses, describes, or defines “tolerance”
PIDWD	Patient information in the package insert discusses, describes, or defines “withdrawal”
PIEqDepAd	Patient information in the package insert equated “dependence” with “addiction”
PIHxDACa	Patient information in the package insert states that the drug should be used with caution in patients with a history of drug abuse
PIMild	The patient information in the package insert was rated to have a mild warning about drug abuse potential
PIMod	The patient information in the package insert was rated to have a moderate warning about drug abuse potential
PISch	The FDA Controlled Substance Schedule is given in the patient information of the package insert
PIStBehW	The patient information of the package insert contains a warning that the drug may cause strange behavior
PIStrong	The patient information of the package insert was rated to have a strong warning about drug abuse potential
PITellMD	The patient information of the package insert instructs the patient to tell his or her doctor if the patient had a history of drug abuse or was currently abusing drugs
PregW	The package insert contains a warning against use in pregnancy
RareAb	The package insert states that abuse of the drug was rare
RareAd	The package insert states that addiction to the drug is rare when used in the medical setting appropriately or that iatrogenic addiction to the drug is rare
RareDep	The package insert states that “dependence” on the drug is rare
RareWD	The package insert states that withdrawal symptoms rarely occur with discontinuation of the drug
Refer	The section dedicated to drug abuse and dependence information refers the reader to another section in the package insert
Restricted	The package insert states that the use of the drug is restricted and gives information on the restrictions for use
S&Eun	Safety and efficacy data for chronic condition are unavailable
SA-	The drug was not self-administered
SAP+	The drug was self-administered by primates
Sch	The FDA Controlled Substance Schedule is given in the package insert
StBehW	The package insert states that strange behavior may occur with use of the drug
Steps	The package insert gives steps to take in order to prevent abuse or diversion of the drug

TimePhD	The package insert estimates how long it takes for physical dependence to occur
TimeTol	The package insert estimates how long it takes to develop tolerance to the drug
TolPtD	The package insert defines a “tolerant patient”
TolPtND	The package insert uses the term “tolerant patient” but does not otherwise define it
TrtAdNoRole	The package insert asserts that the drug has no role in the treatment of drug addiction
TrtODT/N	Treatment of overdose of tolerant and/or non-tolerant patients is described
TrtPhD	The package insert gives information on how to treat physical dependence on the drug
TrtTol	The package insert gives information on how to treat tolerance
TrtWD	The package insert gives information on to treat withdrawal symptoms
Wmild	The researcher rated the warning about drug abuse potential as mild
Wmod	The researcher rated the warning about drug abuse potential as moderate
Wstrong	The researcher rated the warning about drug abuse potential as strong

APPENDIX C**Questionnaire Version 1 of 24**

VCU Medical Center
Virginia Commonwealth University

***Drug Abuse
and
Dependence
Survey***



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Instructions:

You will be presented with 4 case scenarios, each followed by 5 questions about the case.

For scenarios 1-4: Please read the case scenario and package insert information provided. Then answer the questions on the facing page.

After the 4 case scenarios, there are several questions about your views on drug abuse and dependence, sources you might consult for drug information, and characteristics of your practice site. Please answer these questions as instructed for each.

If you have any questions or concerns about this survey, please feel free to contact me via the information on the front cover of this booklet. When you have completed the questionnaire, please return it in the enclosed envelope, and return the postcard separately.

Thank you again for assisting me with my dissertation!

For questions 1-4: Please read the case scenario and package insert information provided. Then answer the questions on the facing page.

1. Case scenario:

A 38 year old Caucasian male is presenting to you with increasing pain, a history of metastatic cancer, and no longer wishes to receive radiation or chemotherapy. The patient has a prior history of psychoactive substance abuse, but has not used in the last 5 years. Previously, another physician has prescribed the medication associated with the following package insert information:

Package Insert Information:

Like other drugs in its class, Drug H can produce drug dependence and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of Drug H. Physical dependence assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy. The rate of development of tolerance varies among patients.

Please mark the box that most corresponds with your opinion.

	Not at all	Not very	Somewhat	Definitely
How comfortable are you with the prior physician's choice?				
How likely are you to refill this prescription?				
How likely would you be to prescribe this medication if you were the first doctor to see this patient?				
How useful do you find this package insert information in making a clinical decision for this patient?				

Based on the package insert information provided on the facing page, what Controlled Substance Schedule do you feel is most appropriate for this medication?

Note: C-II medications are considered to have the highest abuse potential.

C-II C-III C-IV C-V Not controlled

2. Case Scenario

A 38 year old Caucasian male presents to you with complaints of lower back pain that started about 6 months ago. Diagnostic tests have revealed no structural abnormalities. At this time, the cause of the pain is unknown. The patient states that he occasionally uses psychoactive substances for recreational purposes. Previously, another physician has prescribed the medication associated with the following package insert information:

Package Insert Information:

As with other drugs in its class, Drug B may produce psychic dependence, physical dependence, and tolerance may develop upon repeated administration. However, psychic dependence is unlikely to develop when Drug B is used for a short time for the treatment of pain. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, usually assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

Please mark the box that most corresponds with your opinion.

	Not at all	Not very	Somewhat	Definitely
How comfortable are you with the prior physician's choice?				
How likely are you to refill this prescription?				
How likely would you be to prescribe this medication if you were the first doctor to see this patient?				
How useful do you find this package insert information in making a clinical decision for this patient?				

Based on the package insert information provided on the facing page, what Controlled Substance Schedule do you feel is most appropriate for this medication?
Note: C-II medications are considered to have the highest abuse potential.

C-II C-III C-IV C-V Not controlled

3. Case Scenario:

A 38 year old Caucasian male with follows up with you after being seen in the emergency room 3 days ago for a broken ankle. The patient states that he occasionally uses psychoactive substances for recreational purposes. The physician in the emergency room prescribed the drug associated with the following package insert information:

Package Insert Information

Drug F has been associated with severe psychological dependence, physical dependence, and tolerance. However, psychic dependence is unlikely to develop when Drug F is used for a short time for the treatment of pain. Withdrawal symptoms can occur with abrupt discontinuation. Physical dependence assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy.

Please mark the box that most corresponds with your opinion.

	Not at all	Not very	Somewhat	Definitely
How comfortable are you with the prior physician's choice?				
How likely are you to refill this prescription?				
How likely would you be to prescribe this medication if you were the first doctor to see this patient?				
How useful do you find this package insert information in making a clinical decision for this patient?				

Based on the package insert information provided on the facing page, what Controlled Substance Schedule do you feel is most appropriate for this medication?
Note: C-II medications are considered to have the highest abuse potential.

C-II C-III C-IV C-V Not controlled

4. Case Scenario:

A 38 year old Caucasian male presents to you with increasing hip pain from osteoarthritis not relieved by 1000 mg acetaminophen four times daily, nor by 800 mg ibuprofen three times daily. He has no history of psychoactive substance abuse. Previously, another physician has prescribed the medication associated with the following package insert information:

Package Insert Information:

Severe drug dependence and addiction have occurred with Drug C. Addiction is a treatable disease characterized by drug-seeking behavior, craving, and uncontrolled use. Abuse and addiction are separate and distinct from physical dependence and tolerance. Addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Exercise careful record-keeping of prescribing information, including quantity, frequency, and renewal requests. Do not prescribe Drug C for patients who are suicidal or addiction-prone. Prescribe Drug C with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

Please mark the box that most corresponds with your opinion.

	Not at all	Not very	Somewhat	Definitely
How comfortable are you with the prior physician's choice?				
How likely are you to refill this prescription?				
How likely would you be to prescribe this medication if you were the first doctor to see this patient?				
How useful do you find this package insert information in making a clinical decision for this patient?				

Based on the package insert information provided on the facing page, what Controlled Substance Schedule do you feel is most appropriate for this medication?
Note: C-II medications are considered to have the highest abuse potential.

C-II C-III C-IV C-V Not controlled

Please indicate how often you consult the following sources for drug information. The shaded column is for drug abuse and dependence information, and the unshaded column is for other information.

Source Consulted	Never	Yearly	Monthly	Weekly	Daily
Direct contact with manufacturer					
Drug Information Center					
Internet Source					
Package Insert					
Personal Digital Assistant (PDA)					
Pharmacist					
Physician's Desk Reference (PDR)					
Other					

Please indicate how important each of the following factors are to you in deciding whether to prescribe a particular pain medication for a patient:

Factor	Not at all important	Somewhat unimportant	Somewhat important	Very important
Controlled Substance Schedule				
Definitions of terminology given in package insert				
Patient's history of substance abuse				
Presence of clinical advice in package insert information				
Type of pain being treated				
Warning strength in package insert information				

What do you feel is necessary for the following states to exist? Mark all that apply.

Drug Dependence:

- Abuse
- Craving
- Drug-seeking behavior
- Physical dependence
- Psychological dependence
- Tolerance
- Withdrawal

Addiction:

- Abuse
- Craving
- Drug-seeking behavior
- Physical dependence
- Psychological dependence
- Tolerance
- Withdrawal

Please fill in the following information about your practice:

Your gender: Male Female

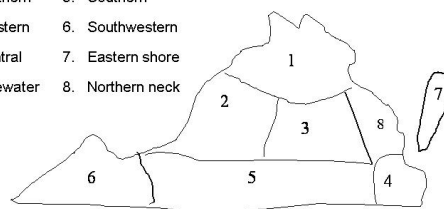
Initial year of licensure: _____

Your specialty: _____

Estimated percentage of your patients who have a known history of substance abuse: _____

Region of Virginia in which you practice:

- 1. Northern
- 2. Western
- 3. Central
- 4. Tidewater
- 5. Southern
- 6. Southwestern
- 7. Eastern shore
- 8. Northern neck



Please feel free to write any additional comments in the space below:

Thank you for your participation!!





Lisa Burroughs Phipps
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APPENDIX D

Patient case scenarios used in survey

Case 1 (No Hx, Cancer pain)

A 38 year old Caucasian male is presenting to you with increasing pain, a history of metastatic cancer, and no longer wishes to receive radiation or chemotherapy. He has no history of psychoactive substance abuse. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 2 (No Hx, CNMP, U)

A 38 year old Caucasian male presents to you with complaints of lower back pain that started about 6 months ago. Diagnostic tests have revealed no structural abnormalities. At this time, the cause of the pain is unknown. The patient has no history of psychoactive substance abuse. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 3 (No Hx, CNMP, K)

A 38 year old Caucasian male presents to you with increasing hip pain from osteoarthritis not relieved by 1000 mg acetaminophen four times daily, nor by 800 mg ibuprofen three times daily. He has no history of psychoactive substance abuse. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 4 (No Hx, Acute)

A 38 year old Caucasian male follows up with you after being seen in the emergency room 3 days ago for a broken ankle. He has no history of psychoactive substance abuse. The physician in the emergency room prescribed the drug associated with the following package insert information:

Case 5 (Past Hx, Cancer pain)

A 38 year old Caucasian male is presenting to you with increasing pain, a history of metastatic cancer, and no longer wishes to receive radiation or chemotherapy. The patient has a prior history of psychoactive substance abuse, but has not used in the last 5 years. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 6 (Past Hx, CNMP, U)

A 38 year old Caucasian male presents to you with complaints of lower back pain that started about 6 months ago. Diagnostic tests have revealed no structural abnormalities. At this time, the cause of the pain is unknown. The patient has a prior history of psychoactive substance abuse, but has not used in the last 5 years. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 7 (Past Hx, CNMP, K)

A 38 year old Caucasian male presents to you with increasing hip pain from osteoarthritis not relieved by 1000 mg acetaminophen four times daily, nor by 800 mg ibuprofen three times daily. The patient has a prior history of psychoactive substance abuse, but has not used in the last 5 years. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 8 (Past Hx, Acute)

A 38 year old Caucasian male follows up with you after being seen in the emergency room 3 days ago for a broken ankle. The patient has a prior history of psychoactive substance abuse, but has not used in the last 5 years. The physician in the emergency room prescribed the drug associated with the following package insert information:

Case 9 (Current use, Cancer pain)

A 38 year old Caucasian male is presenting to you with increasing pain, a history of metastatic cancer, and no longer wishes to receive radiation or chemotherapy. He states that he occasionally uses psychoactive substances for recreational purposes. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 10 (Current use, CNMP, U)

A 38 year old Caucasian male presents to you with complaints of lower back pain that started about 6 months ago. Diagnostic tests have revealed no structural abnormalities. At this time, the cause of the pain is unknown. He states that he occasionally uses psychoactive substances for recreational purposes. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 11 (Current use, CNMP, K)

A 38 year old Caucasian male presents to you with increasing hip pain from osteoarthritis not relieved by 1000 mg acetaminophen four times daily, nor by 800 mg ibuprofen three times daily. He states that he occasionally uses psychoactive substances for recreational purposes. Previously, another physician has prescribed the medication associated with the following package insert information:

Case 12 (Current use, Acute)

A 38 year old Caucasian male follows up with you after being seen in the emergency room 3 days ago for a broken ankle. He states that he occasionally uses psychoactive substances for recreational purposes. The physician in the emergency room prescribed the drug associated with the following package insert information:

APPENDIX E

Package insert excerpts used in survey

(Strong, Advice, No defs)

Drug A (PI#1): Severe dependence has occurred with Drug A. Do not prescribe Drug A for patients who are suicidal or addiction-prone. Prescribe Drug A with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. Tell your patients not to exceed the recommended dose and to limit their intake of alcohol. Many of the Drug A-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs.

(Not strong, No advice, Defs)

Drug B (PI#2): As with other drugs in its class, Drug B may produce psychic dependence, physical dependence, and tolerance may develop upon repeated administration. However, psychic dependence is unlikely to develop when Drug B is used for a short time for the treatment of pain. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, usually assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

(Strong, Advice, Defs)

Drug C (PI#3): Severe drug dependence and addiction have occurred with Drug C. Addiction is a treatable disease characterized by drug-seeking behavior, craving, and uncontrolled use. Abuse and addiction are separate and distinct from physical dependence and tolerance. Addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Exercise careful record-keeping of prescribing information, including quantity, frequency, and renewal requests. Do not prescribe Drug C for patients who are suicidal or addiction-prone. Prescribe Drug C with caution for patients taking tranquilizers or antidepressant drugs and patients who use

alcohol in excess. Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.

(Strong, No advice, Defs)

Drug D (PI#4): Drug D has a high addiction potential and is subject to criminal diversion. Drug addiction is a disease characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is treatable utilizing a multi-disciplinary approach, but relapse is common. Addiction is separate and distinct from physical dependence and tolerance. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy. Upon abrupt discontinuation of Drug D, withdrawal symptoms may occur. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations.

(Not strong, Advice, Defs)

Drug E (PI#5): Drug E may induce psychic and physical dependence. Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with a prior history of dependence. The risk in patients with substance abuse has been observed to be higher. Drug E is associated with craving and tolerance development. Do not discontinue Drug E abruptly, as withdrawal symptoms can occur. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Should withdrawal symptoms occur, reinstitute therapy with Drug E then follow with a gradual, tapered dose reduction of the medication combined with symptomatic support.

(Strong, No advice, No defs)

Drug F (PI#6): Drug F has been associated with severe psychological dependence, physical dependence, and tolerance. However, psychic dependence is unlikely to develop when Drug F is used for a short time for the treatment of pain. Withdrawal symptoms can occur with abrupt discontinuation. Physical dependence assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy.

(Not strong, Advice, No defs)

Drug G (PI#7): Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of Drug G. Tell your patients not to exceed the

recommended dose and to limit their intake of alcohol. Should withdrawal symptoms occur upon discontinuation, reinstitute therapy with Drug G then follow with a gradual, tapered dose reduction of the medication combined with symptomatic support.

(Not strong, No advice, No defs)

Drug H (PI#8): Like other drugs in its class, Drug H can produce drug dependence and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of Drug H. Physical dependence assumes clinically significant proportions only after several weeks of continued use, although some mild degree of physical dependence may develop after a few days of therapy. The rate of development of tolerance varies among patients.

APPENDIX F

Physician feedback from pilot

Too much reading.

Warning for case 2 is too long.

Put more pity factor in letter to get better response since you aren't paying us.

Questions for cases look like I'm going to have to fill out a grid.

Packet looks large and intimidating. Put in letter that there are only 5 questions for each case scenario.

Too many cases if you aren't paying us, or they are too long.

Letter says that you are focusing on package insert information but there are really only a couple of questions about it in the questionnaire. Makes me wonder what you are really after.

Make cases and warnings shorter or give fewer. I probably wouldn't answer more than 3 or 4.

Don't like the font on the cover page.

Will it be in color (printer didn't have color but file was in color).

Too much about postcard/envelope procedure, and not enough about what to expect from the questionnaire itself.

Giving essentially the same three cases twice and only changing the sex makes one of your hypotheses obvious, and it has nothing to do with package insert information. Why are you asking this?

More on format of questionnaire in letter because the packet looks like it's more work than it really is.

Explain that C-II is highest abuse liability. I didn't know what the question was asking because I am not familiar with the schedules.

Looks like you are asking about too many factors and variables...is there any way you can cut some of these out? Are they all necessary?

Layout is fine, maybe a booklet would be better if you could cut out some of the wordiness; put the letter on letterhead.

Make sure you personally sign all the letters – it makes it more personal and they are more likely to fill it out.

APPENDIX G

Survey cover letter, initial package

***Note:** Original cover letter was on letterhead and formatted to fit onto one page.

January 6, 2006

Dear Dr. _____,

I am writing to ask your help with a survey I am conducting for my ***dissertation research project*** at Virginia Commonwealth University's School of Pharmacy. I am interested in exploring physicians' opinions about substance abuse information provided in package inserts.

I am contacting a random sample from a registry of physicians in the state of Virginia who are in various practice settings.

Enclosed in this packet are the questionnaire, an addressed and stamped envelope for its return, and a postcard, also addressed and stamped. The purpose of this postcard is to ensure that all responses are completely anonymous and to prevent repeat mailings. Once your post-card is received, your information will be deleted from the mailing list. The questionnaire should be mailed separately from the postcard.

The questionnaire consists of 4 case scenarios with 5 short questions, and then some requested information about your views on addiction and dependence, sources you consult for information, and general demographics. There are no correct or incorrect answers, as I am interested in your opinions on topics related to drug abuse and dependence information.

This survey is voluntary, and you would help me a great deal with my dissertation by taking approximately 15 to 20 minutes to fill out and return the enclosed questionnaire. If you have any questions or comments about the questionnaire or the survey study, please feel free to contact me, either by phone at (804) 828-6096, or by email at burroughslr@vcu.edu.

Thank you very much for assisting me with my dissertation research!

Sincerely,

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Virginia Commonwealth University
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APPENDIX H

Follow-up cover letter for survey

***Note:** Follow-up cover letter was sent on letterhead and formatted to fit onto one page.

February 10, 2006

Dear Dr. _____,

About four weeks ago, you should have received in the mail a questionnaire about drug dependence and addiction. To the best of my knowledge, I have not yet received your completed questionnaire.

As you may remember from the initial letter, I am writing to ask your help with a survey I am conducting for my *dissertation research project* at Virginia Commonwealth University's School of Pharmacy. I am interested in exploring physicians' opinions about substance abuse information provided in package inserts. You were randomly selected from a registry of physicians in the state of Virginia who are in various practice settings.

I have provided you with a replacement questionnaire in case you no longer have the original but would like to provide responses. Also enclosed are an addressed and stamped envelope for returning the completed questionnaire, and a postcard, also addressed and stamped. The purpose of this postcard is to ensure that all responses are completely anonymous and to prevent repeat mailings. Once your post-card is received, your information will be deleted from the mailing list. The questionnaire should be mailed separately from the postcard. This will ensure that responses are anonymous.

The questionnaire consists of 4 case scenarios with 5 short questions, and then some requested information about your views on addiction and dependence, sources you consult for information, and general demographics. There are no correct or incorrect answers, as I am interested in your opinions on topics related to drug abuse and dependence information.

This survey is voluntary, and you would help me a great deal with my dissertation by taking approximately 15 to 20 minutes to fill out and return the enclosed questionnaire. If you have any questions or comments about the questionnaire or the survey study, please feel free to contact me, either by phone at (804) 828-6096, or by email at burroughslr@vcu.edu.

Thank you very much for assisting me with my dissertation research!

Sincerely,

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APPENDIX I

Codebook for SPSS Analysis

SPSS Code	Variable	Values
Resp#	Respondant #	100-2414
QV	Questionnaire version	1-24
Case#	Patient case	1-12
PI#	Package insert excerpt	1-8
PIStr	Strength of warning	0=not strong; 1=strong
PIAdv	Advice in package insert	0=no advice; 1=advice present
PIDefs	Definitions in package insert	0=no definitions; 1=definitions given
PtPain	Type of pain	1=Acute 2=Cancer 3=Chronic, nonmalignant, known etiology (CNMK) 4=Chronic, nonmalignant, unknown etiology (CNMU)
PtHx	Patient substance abuse history	1=No history of substance abuse 2=Prior history of substance abuse 3=Current recreational use
Comf	Comfort level with prior physician's prescription	For questions following scenarios: 0=Not at all
Ref	Refill likelihood	1=Not very
Rx	Prescribe if first physician?	2=Somewhat
Useful	Insert information useful?	3=Definitely
Sch	Physician-rated schedule for drug	2=C-II 3=C-III 4=C-IV 5=C-V 6=not controlled
SrManD	Source manufacturer for DDAD	For sources consulted for drug abuse and dependence information (DDAD), and for other information:
SrMan	Source manufacturer for other info	
SrDICD	Source drug info ctr for DDAD	0=Never
SrDIC	Source drug info ctr for other info	1=Yearly
SrIntD	Source internet for DDAD	2=Monthly
SrInt	Source internet for other info	3=Weekly
SrPID	Source package insert for DDAD	

SrPI	Source package insert for other info	4=Daily
SrPDAD	Source PDA for DDAD	
SrPDA	Source PDA for other info	
SrRPhD	Source pharmacist for DDAD	
SrRPH	Source pharmacist for other info	
SrPDRD	Source PDR for DDAD	
SrPDR	Source PDR for other info	
SrOthD	Other sources used for DDAD	
SrOth	Other sources used for other info	
FacCSA	Importance of CSA schedule	Rating importance of factors in clinical decision making:
FacDef	Importance of definitions in insert	0=Not at all important
FacHx	Importance of patient's substance abuse history	1=Somewhat unimportant
FacAdv	Importance of advice in insert	2=Somewhat important
FacPain	Importance of type of pain being treated	3=Very important
FacWarn	Importance of package insert warning strength	
DDAb	Abuse	Necessary for Drug Dependence:
DDCr	Craving	0=no
DDDSB	Drug Seeking Behavior	1=yes
DDPhyD	Physical Dependence	
DDPsD	Psychological Dependence	
DDTol	Tolerance	
DDWD	Withdrawal	
AddAb	Abuse	Necessary for Addiction:
AddCr	Craving	0=no
AddDSB	Drug Seeking Behavior	1=yes
AddPhyD	Physical Dependence	
AddPsD	Psych Dependence	
AddTol	Tolerance	
AddWD	Withdrawal	
MDGender	Physician Gender	0=Female 1=Male
MDLiscYr	Physician Year of initial licensure	1940-2005
MDSpec	Physician Specialty	Entered as text
MDHxPer	Estimated percent of patients with known substance abuse history	0-100
MDRegion	Physician practice region	1=Northern 2=Western 3=Central 4=Tidewater 5=Southern

		6=Southwestern 7=Northern Neck 8=Eastern Shore
MDLiscYrMV	Licensure year with median inserted for missing variables	1940-2005
MDhXPerMV	Estimated percent of patients with known substance abuse history with median inserted for missing variables	0-100
DumPnAcute	Indicator for acute pain	0=not acute pain 1=acute pain
DumPnCancer	Indicator for cancer pain	0=not cancer pain 1=cancer pain
DumPnCNMK	Indicator for CNMK	0=not CNMK 1=CNMK
DumHxPast	Indicator for past substance abuse history	0=not a past history 1=past history
DumHxCurr	Indicator for current substance use	0=not a current user 1=current user
MDSpecNum	Numerical category assignment for medical specialty	0=Emergency medicine 1=Family practice 2=Internal medicine 3=Other
DumMDSpecFP	Indicator for family practice	0=not family practice 1=family practice
DumMDSpecIM	Indicator for internal medicine	0=not internal medicine 1=internal medicine
DumMDSpecOth	Indicator for other specialty	0=not "other" specialty 1=other specialty
NewRegion	Collapsed category assignments for practice region	0=Southwestern 1=Northern, Central, or Tidewater (Urban) 2=Western, Southern, Northern Neck, or Eastern Shore (Other rural)
DumReg1	Indicator for urban region	0=not urban 1=urban
DumReg2	Indicator for other rural region	0=not "other rural" region 1=other rural region
MDratedStr	Physician rated strength of package insert warning	0=not C-II 1=C-II
DumUseful	Indicator for usefulness of package insert information	0=not useful (not at all or not very) 1=useful (somewhat or definitely)
DVScale	Willingness to prescribe	Score=Comfort+Refill+Rx

IntAcPast	Acute pain, Past history	Interaction terms are products for indicator variables of pain type and substance abuse history. Example: Acute*Past 0=not acute pain and past history 1=acute pain and past history
IntAcCurr	Acute pain, Current use	
IntCanPast	Cancer pain, Past history	
IntCanCurr	Cancer pain, Current use	
IntCNMKPast	CNMK, Past history	
IntCNMKCurr	CNMK, Current use	
IntStrPast	Strong warning, past history	Interaction terms are products for indicator variables warning strength and substance abuse history
IntStrCurr	Strong warning, current use	
IntStrAc	Strong warning, acute pain	Interaction terms are products for indicator variables warning strength and pain type
IntStrCan	Strong warning, cancer pain	
IntStrCNMK	Strong warning, CNMK	

APPENDIX J

Respondent comments

Note: Most respondents did not make additional comments. Comments that were made are quoted below.

“Good luck!” (Four respondents wrote this)

“Good luck on your research! ☺”

“As previously noted, the package inserts are given to the patient and seldom carried by the patient for the prescribing physician’s review. Physicians are familiar with most all analgesic medications and controlled substances with regard to their potential for dependence/abuse. Decisions regarding what strength of pain medication to use is multifactorial. Your first case scenario did not state what type metastatic cancer or what type pain the patient was experiencing or anticipated length of life expectancy. Scenario 3 involved an ankle fracture which after splinted should not be extremely painful after 3 days; whereas arthritis (scenario 4) can be extremely painful depending on the type arthritis and degree of swelling. Best wishes to you!”

“1) History of drug abuse/dependence should not deter a physician from treating acute pain that is moderately severe or greater. More appropriate would be smaller # pills/prescription. Close follow-up, planned duration of treatment, etc.” 2) For patients with chronic pain, use of contracts between physician and patient can be helpful.”

“I tried to answer as if I were back in private practice. As an ER doc, I’m LESS likely to rx highly controlled, MORE likely to be faced with DSB, and more likely to alleviate suffering short-term (visit only) rather than Rx’ing meds that should be managed by a 1° MD. I don’t write controlleds for chronic pain except terminal patients and will point to package inserts in my explanation to patients.”

“- Package inserts often based on initial FDA studies and not reflections of general clinical practice. – They are useful for initial start-up use and occasional to look up side effects, warnings (preg risks, etc). I find I use them less and less. – The scenarios are

hard to judge as I need more details (lots more) and need to know the particular drug to really be able to make any decisions.”

“I am an internist who practices in the field of addiction treatment, therefore tolerance and physical dependence do not equal your definitions to me. Drug abuse = misuse. Drug dependence = addiction”

“I would be interested in reading a copy of your research results if available. Thanks.”
(Note: this physician signed the comment but it is not readable!)

“Each patient is different. Each doctor is different. Each pain is different. Package inserts are helpful re: pharmacokinetics but worthless re: pharmacodynamics. Your survey falls into the realm of not enough depth to be helpful but enough data to be dangerous!”

“Good luck with your dissertation – would love to know your interpretation of data and conclusions – let us know if you can.” (Note: this note was unsigned)

“Good luck, Lisa, and don’t forget to have fun.”

“Regarding the question of drug dependence, neither physical or psychological dependence are necessary, but each are sufficient to make the diagnosis of dependence.”

“The DEA definitions of drug dependency are very scant and need to be simplified, so they can be useful to clinicians. Your definitions are a lot more detailed and useful alerting the physicians to the very real concerns of dependence for commonly prescribed drugs.”

“The scenarios presented are helpful. There are many situations not discussed that may or may not be deserving of study. These are individuals with criminal behavior, untreated psychiatric states, etc. These should be referred to the drug abuse clinics for thorough examination/treatment. Thank you for the opportunity to be of service.”

“I do not prescribe controlled substances in A/I practice, but your questions made me realize I how much I encounter this problem although it raises suspicion on some phone calls of denied meds. Good luck.”

“In ER practice prescription of drugs with potential for addiction/dependence is quite limited. When they are prescribed for pain only small amounts are usually prescribed.”

“I do not prescribe pain Rx to any sig °. I refer those people to pain tx ctr.”

“Prescription fraud laws should be tougher!”

“Your questions were good but don’t cover all situations – for example, depending on the type of remote history of drug abuse, one might consider a short course of narcotics e.g. 2-3 days for someone with a broken ankle...for people with chronic pain, one would not do this. Good luck with your dissertation!”

“Thank you, Lisa, for exploring these issues! Please go deeply into this whole issue. Adequate pain control in our institutions/hospice programs/at home...in brig...everywhere, is a big, big issue for us all. Try to separate the so-called ‘moral issues’ from the behavioral and factual issues as much as possible. Good luck w/ your degree!”

“The package insert questions may be skewed by the fact that in my practice I rarely see package inserts.”

“Narcotics contract and log sheets have been real helpful to help in dealing with chronic use of controlled substances for pain, etc.”

“The choice to prescribe the same med as presented in the case may have been made easier if the patient had previously experienced relief while on this pill. For instance, in case #3, if that had been included, I’d have ✓ed definitely.” (Note: Case #3 for this questionnaire was cancer pain, prior history, drug A)

“Hope this has been helpful. Pain (chronic) management is a very complex assignment. Good luck with this project.”

“1. I will prescribe a non Class II and class III analgesic if the clinical condition is known and duration of use will be for less than 2 weeks. 2. For any patient presenting

with a pain issue, a full work-up to pinpoint the etiology is first and foremost. Given no dx – I will consider referral to a pain specialist (this step occurs after a rigorous search (work-up) for the etiology of the pain. 3. In your 1st case, a hx of metastatic CA is not enough. The CA must be proven and documentation in my hands. Then I would prescribe but referer to a pain specialist ASAP and not manage the patient’s pain state.” (Note: Case #1 for this questionnaire was cancer pain, no history, Drug A)

“My approach is to always refer pain syndromes to a pain specialist if there is no specific clear reason of pain. I will treat self-limited pain associated with a specific clear dx that would be self-limited. Any cancer-associated pain management is referred to heme/onc. Palliative terminal pain management is coordinated with Hospice. Chronic pain syndromes are always referred to a chronic pain management group or clinic.”

“My patients are all institutionalized due to mental retardation – hence drug/substance abuse is very rare. I’m not too familiar with the Controlled Substance Schedule, but know from experience the degree of potential dependence and addiction associated with the limited number of analgesics I use. Drugs of abuse often make people feel better – at least in the short-term – than psychotropic drugs. If from a public health perspective our society is in some ways ‘toxic’ to our psychological well being (lack of a sense of belonging, lack of community, alienation, lack of social cohesions), then drug abuse is a symptom not only of an individual’s psychic ‘discomfort,’ but of the society’s ‘sickness.’ See Richard Wilkinson’s ‘Unhealthy Societies.’”

“ – Pain should be treated appropriately. – Know your patient (in practice for 1 month or 20 years, etc). – Document reasons (objective) for pain evaluation. – Document benefits of therapy. – Follow up and careful monitoring. – Get family involved. – Etc etc.”

“I avoid even narcotic cough medications when possible.”

APPENDIX K**Statistics for regression models****For Comfort model:**

Predictor	Variable	B	Std error	p-value
Physician gender		-0.093	0.066	0.157
Licensure year		0.011	0.002	<0.001
% pts with history		0.000	0.002	0.908
Practice region	Urban	0.091	0.091	0.317
	Other rural	0.166	0.103	0.106
Medical discipline	Family practice	-0.335	0.081	<0.001
	Internal medicine	-0.342	0.082	<0.001
	Other	-0.306	0.108	0.005
Type of pain	Acute	1.125	0.129	<0.001
	Cancer	1.437	0.126	<0.001
	CNMK	0.243	0.134	0.070
History of abuse	Past	-0.423	0.127	0.001
	Current	-0.500	0.132	<0.001
Warning strength		-0.270	0.053	<0.001
Advice present		-0.169	0.053	0.002
Definitions given		-0.196	0.053	<0.001
Interaction terms	Acute*Past	-0.355	0.182	0.051
Pain*History	Acute*Current	0.198	0.183	0.280
	Cancer*Past	0.414	0.183	0.024
	Cancer*Current	0.364	0.183	0.047
	CNMK*Past	0.313	0.184	0.088
	CNMK*Current	0.086	0.188	0.649

For Refill model:

Predictor	Variable	B	Std error	p-value
Physician gender		0.040	0.065	0.535
Licensure year		0.011	0.002	0.000
% pts with history		-0.002	0.002	0.287
Practice region	Urban	0.104	0.090	0.251
	Other rural	0.147	0.102	0.150
Medical discipline	Family practice	-0.177	0.080	0.027
	Internal medicine	-0.161	0.081	0.049
	Other	-0.193	0.107	0.072
Type of pain	Acute	0.901	0.128	0.000
	Cancer	1.585	0.124	0.000
	CNMK	0.290	0.133	0.029
History of abuse	Past	-0.281	0.125	0.025
	Current	-0.374	0.131	0.004
Warning strength		-0.252	0.052	0.000
Advice present		-0.103	0.053	0.051
Definitions given		-0.153	0.052	0.003
Interaction terms	Acute*Past	-0.435	0.180	0.016
Pain*History	Acute*Current	-0.113	0.182	0.533
	Cancer*Past	0.244	0.181	0.179
	Cancer*Current	0.176	0.181	0.333
	CNMK*Past	0.133	0.182	0.466
	CNMK*Current	0.001	0.186	0.997

For 1st physician model:

Predictor	Variable	B	Std error	p-value
Physician gender		-0.081	0.066	0.217
Licensure year		0.012	0.002	<0.001
% pts with history		0.002	0.002	0.195
Practice region	Urban	0.132	0.091	0.148
	Other rural	0.231	0.103	0.026
Medical discipline	Family practice	-0.181	0.081	0.025
	Internal medicine	-0.239	0.082	0.004
	Other	-0.205	0.109	0.061
Type of pain	Acute	1.143	0.129	<0.001
	Cancer	1.389	0.126	<0.001
	CNMK	0.181	0.134	0.178
	History of abuse	Past	-0.370	0.127
	Current	-0.395	0.133	0.003
Warning strength		-0.276	0.053	<0.001
Advice present		-0.175	0.053	0.001
Definitions given		-0.175	0.053	0.001
Interaction terms	Acute*Past	-0.507	0.183	0.006
	Pain*History	Acute*Current	-0.051	0.184
	Cancer*Past	0.376	0.183	0.041
	Cancer*Current	0.273	0.184	0.137
	CNMK*Past	0.224	0.184	0.224
	CNMK*Current	-0.019	0.188	0.920

For Willingness scale model:

Predictor	Variable	B	Std error	p-value
Physician gender		-0.134	0.179	0.453
Licensure year		0.034	0.006	<0.001
% pts with history		<0.001	0.005	0.962
Practice region	Urban	0.327	0.249	0.189
	Other rural	0.546	0.281	0.052
Medical discipline	Family practice	-0.693	0.220	0.002
	Internal medicine	-0.742	0.225	0.001
	Other	-0.710	0.297	0.017
Type of pain	Acute	3.170	0.351	<0.001
	Cancer	4.411	0.343	<0.001
	CNMK	0.713	0.365	0.051
History of abuse	Past	-1.075	0.346	0.002
	Current	-1.269	0.362	<0.001
Warning strength		-0.797	0.145	<0.001
Advice present		-0.448	0.146	0.002
Definitions given		-0.524	0.144	<0.001
Interaction terms	Acute*Past	-1.298	0.497	0.009
Pain*History	Acute*Current	0.025	0.501	0.960
	Cancer*Past	1.034	0.499	0.039
	Cancer*Current	0.816	0.500	0.103
	CNMK*Past	0.670	0.501	0.181
	CNMK*Current	0.067	0.512	0.896

VITA

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PHAR 672: Advances in Mental Health Pharmacy Practice, Spring 2005

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PHAR 743: Pharmacotherapy III, Fall 2005

PHAR 744: Integrated Therapeutics, Spring 2004

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