A NATIONAL SURVEY ON PRESCRIBERS’ KNOWLEDGE OF AND THEIR
SOURCE OF DRUG-DRUG INTERACTION INFORMATION-AN APPLICATION OF
ITEM RESPONSE THEORY

by

Yu Ko

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ABSTRACT

OBJECTIVES: (1) To assess prescribers’ ability to recognize clinically significant DDIs, (2) to examine demographic and practice factors that may be associated with prescribers’ DDI knowledge, and (3) to evaluate prescribers’ perceived usefulness of various DDI information sources.

METHODS: This study used a mailed questionnaire sent to a national sample of prescribers based on their past history of DDI prescribing which was determined using data from a pharmacy benefit manager covering over 50 million lives. The survey questionnaire included 14 drug-drug pairs that tested prescribers’ ability to recognize clinically important DDIs and five 5-point Likert scale-type questions that assessed prescribers’ perceived usefulness of DDI information provided by various sources. Demographic and practice characteristics were collected as well. Rasch analysis was used to evaluate the knowledge and usefulness questions.

RESULTS: Completed questionnaires were obtained from 950 prescribers (overall response rate: 7.9%). The number of drug pairs correctly classified by the prescribers ranged from zero to thirteen, with a mean of 6 pairs (42.7%). The percentage of prescribers who correctly classified specific drug pairs ranged from 18.2% for warfarin-cimetidine to 81.2% for acetaminophen with codeine-amoxicillin. Half of the drug pair questions were answered “not sure” by over one-third of the respondents; among which, two were contraindicated. Rasch analysis of knowledge and usefulness
questions revealed satisfactory model-data fit and person reliability of 0.72 and 0.61, respectively. A multiple regression analysis revealed that specialists were less likely to correctly identify interactions as compared to prescribers who were generalists. Other important predictors of DDI knowledge included the experience of seeing a harm caused by DDIs and the extent to which the risk of DDIs affected the prescribers’ drug selection. ANOVA with the post-hoc Scheffe test indicated that prescribers considered DDI information provided by “other” sources to be more useful than that provided by computerized alert system.

**CONCLUSIONS:** This study suggests that prescribers’ DDI knowledge may be inadequate. The study found that for the drug interactions evaluated, generalists performed better than specialists. In addition, this study presents an application of IRT analysis to knowledge and attitude measurement in health science research.
CHAPTER 1

INTRODUCTION

1.1 Statement of the Problem

Medication use is prevalent in the U.S. and becoming more so. Approximately four-fifths of U.S. adults use at least one medication in any given week and the rate of use increases with age (Kaufman et al. 2002). Based on the 2002 National Ambulatory Medical Care Survey, medication therapy was reported at 577.1 million physician office visits, accounting for 64.8% of all office visits (Woodwell and Cherry 2004). On average, 2.3 medications were ordered or provided at each office visit with any prescription (Woodwell and Cherry 2004). One risk of medication use is the possibility of drug-drug interactions (DDIs). DDIs are an important contributing factor to adverse drug events (ADEs). The clinical impact of DDIs has been documented in the literature, which indicated that DDIs could lead to hospital admissions and emergency department (ED) visits (Prince et al. 1992; Jankel and Fitterman 1993; Stanton et al. 1994; Yee et al. 2005).

Healthcare professionals’ recognition of a potential DDI is essential in reducing the risk of DDIs and potentially drug-related morbidity and mortality. Several studies have been conducted that assess prescribers’ ability to identify clinically significant DDIs. Testing prescribers’ ability to recognize potential DDIs without the use of drug references could help understand the necessity and potential influence of prescribing support systems, such as automated DDI alerts, in reducing DDIs. In addition, a better
understanding of the determinants of prescribers’ ability to recognize DDIs could help identify those prescribers with insufficient DDI knowledge who could be targets of educational intervention.

Given the rate at which new medications are introduced to the market and the diversity of existing drugs, clinicians frequently need to consult information sources when prescribing. There are many sources of information for prescribing but little is known about which are more commonly used in practice by prescribers. Compared to general pharmaceutical information, less is known about prescribers’ sources of DDI information. In addition, there is a gap in understanding of prescribers’ perception about the relative usefulness of these different sources.

Evaluations of prescribers’ knowledge can be performed using self-administered questionnaires. Conventionally, the analysis of knowledge and attitudinal tests in health sciences has been based on the classical test theory (CTT), such as calculating Cronbach’s coefficient alpha to examine a test’s reliability. Despite its importance and popularity, there are some limitations inherent in CTT. For example, with CTT, the estimation of an examinee’s test score is confounded by the difficulty of test items (i.e., the easier the test, the higher the score) (Downing 2003). The emergence of item response theory (IRT) and related models offers an alternative, if not necessarily better, analytical tool that can address a number of limitations inherent in CTT. Given the common use of psychological measurement in health sciences (e.g., satisfaction, clinical competency, health-related quality of life) and the advantages of IRT over CTT, researchers need to familiarize themselves with and consider applying IRT to
test/questionnaire development, refinement, and analysis. In addition, more research needs to be done to examine the increase in information derived from IRT analysis over the conventional analysis based on CTT.

1.2 Purpose of the Research

The purpose of this study was three-fold:

(1) The first objective of this study was to assess the degree to which prescribers could recognize interacting drug-drug pairs. The drug-drug pairs were selected from a list of 25 clinically important DDIs that was developed by an expert panel through a modified Delphi consensus-building process (Malone et al. 2004). Also, factors associated with prescribers’ ability to recognize DDIs were examined.

(2) The second objective of this study was to understand how prescribers are usually informed of their patients’ potential exposure to DDIs and how useful that information source is to the prescriber. For this study, the information source was considered useful if it changed the prescriber’s initial prescribing decisions, was new to the prescriber, or was relevant to the patient, etc. The usefulness of various DDI information sources as perceived by the prescribers was examined in this study.

(3) The third objective of this study was to apply IRT to the development and evaluation of the measure of prescribers’ ability to recognize clinically significant DDIs. Because these knowledge test items were dichotomously-coded (i.e., either wrong or correct), IRT models for dichotomous data were used for knowledge data. The psychometric properties of the test were evaluated on the item level by the application
of IRT. In addition, the use of IRT analysis on the pilot test data aided the selection of items to be used in the final questionnaire. IRT was also used to analyze the attitude assessment items in the questionnaire. Because these items were in a 5-point response format, IRT models for polytomous data were used for attitudinal data.

1.3 Research Objectives

The specific objectives of this research were as follows:

(1) To use IRT to produce a summary score for each prescriber that indicates his/her knowledge of DDIs

(2) To assess whether the prescribers who had prescribed at least one interacting drug combination had a lower mean test score of DDI knowledge than those who had not

(3) To examine whether the prescribers who had prescribed at least one interacting drug combination were less likely to answer the DDI of interest question correctly than the matched group of prescribers (i.e., prescribers who had prescribed either one of the medications in the interacting drug pair)

(4) To explore demographic and practice factors that may be related to prescribers’ knowledge of DDIs

(5) To identify prescribers’ most commonly-used source of DDI information

(6) To assess prescribers’ opinions concerning their usual source of DDI information

(7) To examine the relationship between prescribers’ DDI knowledge and their usual source of DDI information
(8) To examine the psychometric properties (e.g., reliability, validity, and dimensionality) of the knowledge and attitudinal tests using IRT

(9) To examine prescribers’ satisfaction with and attitude toward DDI alerts provided in computerized physician order entry systems

1.4 Research Hypotheses

The null hypotheses that were tested in this study are as follows:

Ho1: There is no difference in DDI knowledge between prescribers who had prescribed at least one interacting drug combination and prescribers who had no recent history of DDI prescribing.

Ho2: The prescribers who had prescribed at least one interacting drug combination were equally likely to answer the DDI of interest question correctly as the prescribers who had no recent history of prescribing such an interacting drug combination.

Ho3: There is no difference in DDI knowledge among prescribers who usually consult written, electronic, or personal information source for DDI information.

Ho4: There is no difference among prescribers’ perceptions of the usefulness of pharmacists, computerized alert systems, personal digital assistants (PDAs), or other DDI information sources.

1.5 Definitions and Abbreviations

Drug-Drug Interactions (DDI)

The modification of the effects of one drug by the prior or concurrent administration of
another drug.

**Computerized Physician Order Entry (CPOE)**

A variety of computer-based systems that share the common features of automating the medication ordering process to ensure standardized, legible, and complete orders.

**Classical Test Theory (CTT)**

The leading framework for analyzing and developing standardized tests. The essence of the theory is that any observed test score can be partitioned into a true score and a random error; therefore, the theory is sometimes called the true score theory.

**Item Response Theory (IRT)**

A statistical theory consisting of mathematical models that enable predictions of how examinees at different ability levels on a latent trait should respond to a test item.

**Construct**

The dimension that the measure is intended to assess. In this dissertation, the terms “construct”, “trait”, and “attribute” will be used interchangeably.

**Interval scale**

An interval scale of measurement consists of an ordered set of categories, and the categories form a series of intervals that are all exactly the same size. As a result of the
scale properties, addition and subtraction of the scale points are permissible operations.

**Other abbreviations**

ADE = adverse drug event  
ADR = adverse drug reaction  
AHFS = American Hospital Formulary Service  
ANOVA = analysis of variance  
AzCERT = Arizona Centers for Education and Research on Therapeutics  
CAM = complementary and alternative medicine  
CASS = coding accuracy support system  
CAT = computer-adaptive testing  
DEA = Drug Enforcement Agency  
DIF = differential item functioning  
DRMM = drug-related morbidity and mortality  
ED = emergency department  
EMQ = extended matching question  
FDA = Food and Drug Administration  
GP = general practitioner  
G-PCM = generalized partial credit model  
GRM = graded response model  
IRB = institutional review board  
MNSQ = mean-square
NCOA = national change of address
NP = nurse practitioner
NSAID = nonsteroidal anti-inflammatory drug
OTC = over-the-counter
PA = physician assistant
PBM = pharmacy benefits management
PCM = partial credit model
PDA = personal digital assistant
PDR = Physicians’ Desk Reference
Pharm.D. = Doctor of Pharmacy
RCT = randomized clinical trial
RSM = rating scale model
Rx = prescription
SEM = standard error of measurement
USPS = U.S. Postal Service
VA = Veterans Affairs
VAMS = Veterans Affairs medical center
1-PL = 1-parameter logistic
2-PL = 2-parameter logistic
3-PL = 3-parameter logistic
CHAPTER 2
LITERATURE REVIEW

2.1 Drug-Drug Interactions

This section begins with an introduction of the definitions and mechanisms of DDIs. Previous studies of DDI rates conducted in various healthcare settings will then be reviewed, followed by a summary of the studies that examined the clinical impact of DDIs. Because the specific economic impact of DDIs is largely unknown, the costs of drug-related morbidity and mortality, which can result from DDIs, will be described. Finally, several issues in conducting studies related to DDI will be discussed.

2.1.1 Definitions and Mechanisms

The response to a drug may be altered by the concurrent administration of other substance intake. As defined by Stockley, a drug interaction occurs when the effects of one drug are changed by the presence of another drug, food, drink, or by some environmental chemical agent (Stockley 1999). Based on this definition, a drug-drug interaction occurs when the effects of one drug are altered because of the presence of another drug. Following this definition, the outcome of an interaction can be harmful or beneficial (Stockley 1999). Similarly, Hartshorn defined a DDI as the modification of the effects of one drug by the prior or concurrent administration of another drug(s) (Hartshorn 1976). Another definition of DDI, which focuses more on clinical aspects, is the modification of the diagnostic, preventive, therapeutic, or other action of a drug in or
on the body by another drug (Martin 1978). Other researchers have applied a definition that emphasized the adverse consequence of DDIs; a DDI is a pharmacokinetic or pharmacodynamic influence of drugs on each other, which can result, in addition to desired effects, in reduced effectiveness or increased toxicity (Becker et al. 2005).

The mechanisms by which drugs may interact can be categorized as pharmacokinetic, pharmacodynamic, and combined toxicity (Hansten 2001). Pharmacokinetic interactions occur when the absorption, distribution, metabolism, or excretion process of a drug is altered by concurrent use of other drugs (McInnes and Brodie 1988; Hansten 2001). These are called ADME interactions (Stockley 1999). Among these four pharmacokinetic mechanisms, metabolism, which involves either induction or inhibition of the hepatic monooxygenase enzyme system, has been considered the most important factor leading to clinically significant DDIs (Ajayi et al. 2000). An example of pharmacokinetic interaction is the enhanced and prolonged blood glucose-lowering effect of repaglinide because of the coadministration of gemfibrozil (Scheen 2005).

Pharmacodynamic interactions are interactions where the action of drugs in the body is modified when drugs which act at the same site or on the same physiological system are used concurrently (Avery 1977). As an example of this type of interaction, naproxen interferes with the inhibitory effect of aspirin on platelet cyclooxygenase-1 activity and function (Capone et al. 2005). Combined toxicity refers to the increased likelihood of organ damage when both of the concurrently-used drugs have toxic effects on the same organ (Hansten 2001). For example, kidney damage can be produced by the coadministration of two nephrotoxic drugs, even though the dose of either drug alone
may be insufficient to produce toxicity (Hansten 2001).

2.1.2 Rates of DDIs

Most studies of DDI rates have been conducted in emergency department (ED) or inpatient settings. Adverse interactions between drugs prescribed during ED visits are particularly worrisome because there is often no follow-up, and if there is a follow-up visit, it is usually with a different physician (Beers et al. 1990; Heininger-Rothbucher et al. 2001). For example, Beers et al. evaluated 424 randomly selected ED visits to a university-affiliated hospital (Beers et al. 1990). Their findings suggested that potential DDIs were introduced by the changes made in medical regiments during the ED visit for 4.7% of the subjects (Beers et al. 1990). In a 1992 prospective study, Herr et al. reported that the incidence of clinically relevant DDIs was significantly higher among current medications (9.7%) than medication added in the ED (3.1%) (Herr et al. 1992). Similar findings were reported in a European study, with a DDI incidence of 6.4% at the time of presentation to an ED and 3.8% during the ED visit (Heininger-Rothbucher et al. 2001). In a more recent study, 25% of ED outpatients had at least one DDI at the time of arrival, and 5% of those who received medication during their ED visit had a DDI added by the treating ED physician (Gaddis et al. 2002). With the use of a computerized drug-interaction program, Egger and colleagues found that 60.0% of inpatients had at least one potentially interacting drug combination at discharge (Egger et al. 2003a).

Elderly people are at a high risk of DDIs because they are more likely to suffer from more than one disease concurrently, have pharmacokinetic changes, and take several
different drugs at one time. The rate of a potential DDI in elderly patients who were prescribed a new medication during their ED visit was found to be 2.7% (Hancock et al. 1992). A study of an ED high-risk population (i.e., patients receiving three or more medications and patients 50 years of age or older taking at least two medications) indicated that 47% of the patients had a DDI, with half of these DDIs due to medications related to ED treatment (Goldberg et al. 1996). A retrospective chart review of ED visits made by patients 65 years of age and older suggested that potential DDIs were present in 31.1% of patients’ medication regimens (Hohl et al. 2001). The occurrence of DDIs in nursing homes has been estimated to be around 6% of the medications used (Cooper et al. 1975; Mamun et al. 2004). In geriatric inpatients, the occurrence of DDIs has been estimated to be between 14.7 and 60.2% of the patients studied (Doucet et al. 1996; Egger et al. 2003b).

Epidemiological studies in community settings worldwide have generated a wide range of estimates regarding the occurrence of potential DDIs. A Swedish study conducted in a primary care setting showed that potential DDIs occurred in 1.9% of all prescriptions and in 12% of patients who received two or more drugs concurrently (Linnarsson 1993). Another study from Sweden found 13.6% of the prescriptions dispensed by all Swedish pharmacies included at least one potential drug interaction (Merlo et al. 2001). A recent study was conducted by Bjorkman et al. to detect the frequency of potential DDIs in elderly outpatients in six European countries (Bjorkman et al. 2002). Forty-six percent of the elderly population had at least one drug combination possibly leading to a DDI and on average there were 0.83 potential DDIs per person (Bjorkman et al. 2002). The
prevalence reported in this study was higher than that in other outpatient studies, probably because some commonly-used recommended drug combinations were included and the study patients used more drugs on average than other study patients (Bjorkman et al. 2002). More recently, a large-scale study of outpatients in France showed that 0.28% of prescriptions involved medications that were contraindicated, or the most serious DDIs (Guedon-Moreau et al. 2004).

In the US, several studies have been conducted in recent years to examine the frequency of potential DDIs for specific drug pairs in the ambulatory care setting. Claims databases were commonly used in these studies. In an analysis of data from a pharmacy benefits management (PBM) program that covers approximately 2.9 million patients, the overall incidence of potentially serious DDI combinations was estimated at 12.1% and 3.2% before and after systematic software filters were applied, respectively (Peng et al. 2003). Solberg and colleagues studied the frequency of 44 potential DDIs in the members of two large health plans (Solberg et al. 2004). Their study findings showed that the rate of members with at least one potential DDI increased from 2.04% in 1998 to 2.32% in 2001 (Solberg et al. 2004). Similarly, Malone et al. reported that 374,000 of 46 million plan participants had been exposed to at least one of the 25 clinically important DDIs evaluated, yielding a prevalence of 0.8% of study patients (Malone et al. 2005). Another study using claims data examined the frequency of 47 DDIs that involved one of five object medications (i.e., warfarin, digoxin, cyclosporine, lovastatin, and simvastatin) (Lafata et al. 2006). The proportion of patients who were dispensed a DDI pair on the same day ranged from 7.1% to 17.7%, depending upon the
object medication (Lafata et al. 2006). Lastly, Zhan and colleagues conducted a retrospective analysis of elderly outpatient visits in two national surveys and found that 0.74% of the visits with two or more prescriptions had at least one of the six potentially inappropriate drug-drug combinations examined in their study (Zhan et al. 2005).

### 2.1.3 Clinical and Economic Impact

Previous studies have demonstrated that ADEs, which can result from DDIs, are a significant cause of death, hospital admission, and prolonged length of stay in hospitals (Col et al. 1990; Einarson 1993; Stanton et al. 1994; Gray et al. 1998; Lazarou et al. 1998; Malhotra et al. 2001; Rodriguez-Monguio et al. 2003). The reported proportion of ADEs or adverse drug reactions (ADRs) that could be attributed to DDIs varied in previous studies. In an analysis of a hospital’s ADR database, Winterstein and colleagues reported that 25.6% of preventable ADRs were associated with DDIs (Winterstein et al. 2002). Similarly, an investigation of hospital admissions resulting from ADRs suggested that DDIs were associated with 26% of the preventable ADRs (McDonnell and Jacobs 2002). In hospitalized patients, DDIs were found to be related to 2.7-2.8% of preventable ADEs (Kanjanarat et al. 2003). A more recent study of inpatients demonstrated that ADEs commonly occurred due to various drug interactions, with additive DDIs (i.e., two or more drugs with similar physiologic effects) accounting for 39% of the ADEs (Nebeker et al. 2005). In a study of ADEs in the ambulatory setting, DDIs were found to account for 13.3% of the errors identified in the prescribing stage (Gurwitz et al. 2003). An analysis of ADE case reports published in *Clin-Alert*
indicated that DDIs contributed to 11% of drug-induced threats to life, 8% of significant ADEs, 6% of fatal ADEs, and 2% of drug-induced permanent disabilities (Kelly 2001a; 2001b; 2001c; Marcellino and Kelly 2001).

The clinical impact of DDIs has been documented in the literature. A review of the literature examining the impact of DDIs on hospitalization rates found that up to 2.8% of hospital admissions were caused by DDIs (Jankel and Fitterman 1993). A study conducted in Australia indicated that almost 10% of hospital admissions were drug-related, among which 4.4% were due to DDIs (Stanton et al. 1994). The incidence of DDIs may have been underestimated because of the inability to identify a DDI as the cause of the adverse outcome and the incorrect ascription of a DDI-caused problem to only the last prescribed drug (Becker et al. 2005). A matched-pair case-control study found that exposure to a number of DDIs was associated with a significantly increased risk of hospitalization (Hamilton et al. 1998). Similar results were reported in a recent study published by JAMA, which demonstrated that the presence of specific DDIs was associated with up to a 20-fold increase in the risk of hospital admission for drug toxicity among elderly patients (Juurlink et al. 2003). With regard to ED patients, a recent study of Veterans Affairs (VA) elderly patients reported that 12.6% ED visits were associated with drugs, among which 3% resulted from DDIs (Yee et al. 2005). A lower estimate was reported in a prior study, with 2.9% of ED visits due to drug-related illnesses, among which only 1% resulted from DDIs (Prince et al. 1992). Although the frequency of DDIs leading to an ED visit was low, this type of event was more severe because most of these patients were hospitalized (Raschetti et al. 1999).
Little is known about the economic impact of DDIs on health care. However, literature has shown that the economic impact of drug-related morbidity and mortality (DRMM), which can be a result of DDIs, is substantial. Annual costs attributable to ADEs in a typical tertiary care hospital were approximated to be $1.1-5.6 million (Bates et al. 1997). A review of studies addressing the economic consequences of drug morbidity indicated that patients who developed ADEs were hospitalized an average of 1.2-3.8 days longer than those who did not, with additional hospital costs of $2,284-5,640 per patient (2000 dollars) (Rodriguez-Monguio et al. 2003). A more recent study indicated that drug-induced ED visits cost a VA hospital an estimated $1.5 million over 12 weeks, with 90% of costs resulting from subsequent hospitalizations (Yee et al. 2005). As indicated by population-based studies, an estimated $76.6 billion in 1995 and an updated estimate of $177.4 billion in 2000 were spent on DRMM in the ambulatory setting, the largest component of which was associated with drug-related hospitalizations (Johnson and Bootman 1995; Ernst and Grizzle 2001). Others have calculated the cost of DRMM in nursing facilities to be $4 billion (Bootman et al. 1997).

2.1.4 Issues in DDI-Related Research

While identifying potential DDIs is essential in pharmaceutical therapy, unfortunately, no one list of DDIs is agreed-upon, let alone which DDIs are usually clinically significant. The discrepancies among different information sources of DDIs have been documented in the literature. In a comparison of five leading sources of DDI information, study results suggested that there were discrepancies in both listing and clinical significance ratings for
DDIs and the extent of agreement varied depending on drug classes (Fulda et al. 2000). Abarca and colleagues found little agreement among four commonly used DDI compendia regarding the designation of which interactions have the greatest clinical importance (i.e., major DDIs) (Abarca et al. 2004). Surprisingly, only 2.2% of the major DDIs were listed in all four compendia and the majority of interactions (71.7%) were listed in only one compendium (Abarca et al. 2004). A similar study on dermatologic drugs also found considerable discrepancies among the four US compendia with respect to the number of DDIs listed (Chao and Maibach 2005).

In the literature, most studies of DDI rates only examined the occurrence of DDIs in prescriptions and little attempt was made to determine the extent to which these potential DDIs actually caused any harm. Although DDI prescribing and dispensing may be common, especially in the elderly population, only a fraction of patients taking interacting drug combinations actually suffer adverse consequences. For example, a study by Doucet et al. found that among 528 older adults who were exposed to at least one DDI, only 130 patients had adverse events (Doucet et al. 1996). Therefore, it is clear that not all potential DDIs are clinically important. Besides, the contraindication between drugs is not always definite. As commented by Malone et al., “Some of the drug pairs involved in the interactions can be used safely if appropriate monitoring is performed or proper instructions are given to the patient” (Malone et al. 2005). In addition, the clinical impact of DDIs may lessen after initial exposure as a result of physiologic compensations or dose adjustments (Beers et al. 1990).

Another concern of DDI research is the imprecise and inconsistent classification of the
clinical significance of DDIs. For instance, Kurfees and Dotson, by chart review, revealed no serious actual DDIs for any patient receiving a potential DDI, even though 27% of the potential DDIs were categorized as highly significant (Kurfees and Dotson 1987). Although the importance of a classification system of the clinical relevance or significance of DDIs is generally agreed upon, several barriers and difficulties exist to the implementation of such a system (Hansten et al. 2001; Preskorn 2005). For example, inadequacies of clinical DDI data constitute a major impediment. It is difficult to gather formal data on the clinical relevance of DDIs due to ethical considerations (Preskorn 2005). The majority of published data on DDIs has come from pharmacokinetic studies of healthy subjects and case reports, with very few epidemiologic studies being conducted (Hansten et al. 2001). As such, it is difficult to estimate how often a particular DDI causes adverse effects (Hansten et al. 2001). Another difficulty is the lack of agreement in determining the clinical relevance of DDIs (Preskorn 2005). In addition, the severity of a DDI is difficult to assess because one DDI can have many possible outcomes depending on the health and physical condition of the patient (Hansten et al. 2001). Given these difficulties, however, attempts have been made to improve the categorization of DDIs. Roberts and colleagues developed a new scale of the clinical significance of DDIs using practicing pharmacists’ judgments (Roberts et al. 1996). Inconsistencies were observed between the developed scale and previously published clinical significance scales (Roberts et al. 1996). More recently, Hansten et al. proposed a classification scheme which took into account the potential severity of the adverse outcome, factors that influence the risk of the outcome, and available management
alternatives (Hansten et al. 2001). In order to make DDI studies more interpretable and comparable, the inconsistencies in the rating of the clinical significance of DDIs need to be addressed.

### 2.2 Healthcare Professionals’ Knowledge of Drug-Drug Interactions

Healthcare professionals’ recognition of a potential DDI is essential in reducing the risk of DDIs and their adverse consequences. As indicated by the results of a 1991 survey, the majority of pharmacy departments in hospitals studied (83%) detected drug interactions using the knowledge of the pharmacist who processed the orders (Elanjian et al. 1993). Prescribers’ ability to identify potential DDIs has been examined in several studies. Based on the feedback from a small group of physicians, Preskorn and colleagues noticed physicians’ dissatisfaction with their ability to understand and avoid DDIs (Preskorn et al. 2002). In a comparison of the performance of physicians who practice in ED settings to that of a computer database in identifying potential DDIs, Langdorf et al. found that when computer software was used as the criterion standard, the performance of both general ED physicians and an expert ED physician was poor, with sensitivities of 14% and 25%, respectively (Langdorf et al. 2000). In a study conducted by Glassman and colleagues, a ten-item DDI test was developed to test clinicians’ familiarity with common DDIs (Glassman et al. 2002). The test contained three contraindicated drug combinations (eg, sildenafil/isosorbide), four pairs with moderate to severe DDIs involving potential alterations in serum levels (eg, theophylline/cimetidine), and three pairs that had no known interaction (Glassman et al. 2002). The study results
indicated that clinicians correctly categorized 44% (range 11–64%) of all drug-drug pairs. In addition, multiple linear regression analyses revealed that being a general internist, being of younger age, and spending more half-days in the clinic were associated with better ability to correctly categorize drug-drug pairs (Glassman et al. 2002). About two years after an electronic medical record system being implemented at the study sites, the same test was administered to the same sample of clinicians in 2002. Study results demonstrated that clinicians correctly categorized similar percentages of the seven interacting drug–drug pairs at baseline and follow-up (53% vs. 54%) but improved their overall recognition of the three contraindicated drug–drug pairs (51% vs. 60%) (Glassman et al. 2006).

Despite the fact that pharmacists have more extensive training in pharmacology, studies evaluating pharmacists’ knowledge have also found a low recall of DDIs. In a study of community pharmacists, only one of the 48 pharmacists notified the prescribing physician of the clinically important DDI studied (i.e., sodium warfarin and phenobarbital) (Nelson et al. 1976). In a study published in 1996, 32% of pharmacies filled prescriptions for erythromycin and terfenadine without any comment, despite letters from the Food and Drug Administration (FDA) warning of this potentially life-threatening interaction (Cavuto et al. 1996). In another study, pharmacists’ ability to identify interactions was found to vary significantly with the number of drugs on the medication profile (Weideman et al. 1999). As the number of drugs in medication profiles increased from two to sixteen, the percentage of DDIs detected decreased from 66% to 17% (Weideman et al. 1999).
With the vast and increasing number of FDA-approved drugs, it is unrealistic to expect healthcare professionals to memorize the established DDIs, let alone the new ones reported each year. An assessment of prescribers’ ability to recognize clinically significant DDIs without referring to reference materials would help us understand the necessity and potential influence of prescribing support systems, such as automated DDI alerts, in reducing DDIs and, consequently, drug-related morbidity and mortality and their associated costs. In addition, more research needs to be done to fill the gap of knowledge regarding the determinants of prescribers’ ability to recognize important DDIs. Such information could help identify those prescribers with insufficient DDI knowledge who could be targets for educational intervention.

2.3 Healthcare Professionals’ Sources of DDI Information

To keep abreast of the ever-unfolding and expanding information about medications, it is essential for healthcare professionals to routinely obtain and process vast volumes of pharmaceutical information. There are many sources of pharmaceutical information available to healthcare professionals, such as journals, books, conferences, colleagues, pharmacists, and pharmaceutical representatives, to name a few. In addition, with the advances in information technology, health practitioners can obtain information from sources such as Micromedex, the Internet, and PDAs, which were not available decades ago. In the 1980s, a study found that the Physicians’ Desk Reference (PDR) and journal articles were frequently consulted by physicians for new drug information (McCue et al. 1986). Different findings were reported in another study of physicians, which indicated
that commercial sources (e.g., pharmaceutical representatives) were cited more often than professional ones (e.g., journals, other doctors) for providing the initial information about a new drug, but the reverse was the case when a physician was actively considering prescribing it (Peay and Peay 1984). Another survey of physicians in the 1980s suggested that physicians were most likely to solicit prescription drug information first from journal articles, followed by colleagues, conventions, sales representatives, and finally pharmacists (Evans and Beltramini 1986a; 1986b). Similar findings were reported in a review of journal articles published from 1978 to 1992, which indicated that physicians preferred to obtain information from journals and books, but also that they often consulted colleagues for clinical and research questions (Haug 1997). A literature review published in 1991 demonstrated that physicians' sources of pharmaceutical information had changed (Williams and Hensel 1991). The authors concluded that in general, commercial sources appeared to have declined in importance and preference whereas journal articles had not changed in importance, remaining the most preferred source of information (Williams and Hensel 1991). Different preferences were expressed by other types of health practitioners. As suggested by the results of a survey of physician assistants (PAs), Doctors of Pharmacy (Pharm.Ds.) were ranked the highest as being good sources of drug information, followed by journal articles, physicians, non-Pharm.D. pharmacists, detailed persons, and finally PAs (Fincham 1986).

More recently, a physician survey conducted in the UK indicated that, compared to electronic references and other sources, paper-based formularies were the most common source of information about drug dosing (Franke et al. 2000). Nevertheless, most
physicians viewed computerized decision support as potentially useful (Franke et al. 2000). McGettigan et al. surveyed a group of prescribers to examine the importance of their information sources for prescribing drugs (McGettigan et al. 2001). The study results suggested that among general practitioners (GPs), the Drugs and Therapeutics Bulletin and medical journal articles were the sources most frequently rated as important; however, pharmaceutical representatives and hospital/consultant recommendations were the sources where 78% of the GPs derived information about the last new drug prescribed (McGettigan et al. 2001). In this study, hospital doctors differed from GPs regarding their prescribing information sources. Among hospital doctors, both the British National Formulary and senior colleagues were of the greatest theoretical importance while in practice, information on their most recently prescribed drug was derived from a broad range of sources, with senior colleagues being the most commonly reported (29%) (McGettigan et al. 2001).

Compared to general pharmaceutical information, less is known about healthcare professionals’ sources of DDI information. Strain and colleagues recommended several sources for DDI information: MEDLINE, Reactions, Micromedex, Physicians Desk Reference, and American Hospital Formulary Service Drug Information (Strain et al. 2001). A new source for clinicians to DDI information is via PDA DDI software, including DrugIx, iFacts, ePocrates Rx, Lexi-Interact, Tarascon pocket Pharmacopoeia. Several evaluations were conducted on PDA DDI software programs (Barrons 2004; Robinson and Burk 2004; Perkins et al. 2006). Due to differences among studies in evaluation criteria, DDI pair selection, and DDI software program inclusion, mixed
conclusions were reached with regard to which software most excelled in assessing DDIs.

In a survey by McAuley and colleagues, most primary care physicians surveyed used themselves as their primary information source for drug interaction screening but a significant number preferred to use pharmacists as the source of such information (McAuley et al. 1999). Ko and colleagues surveyed prescribers and pharmacists in VA medical centers about their most frequently used sources of general drug and DDI information. (Ko et al. 2007). The study results indicated that electronic references (e.g., MicroMedex, Internet, PDA, UpToDate) were most frequently used by both prescribers and pharmacists. The next most frequently used source for prescribers was pharmacists, whereas for pharmacists, it was printed references (e.g., AHFS Drug Information, Facts & Comparisons). These results were similar for both general drug information and DDI information. However, the results indicated that prescribers relied more heavily on pharmacists to obtain DDI information relative to general drug information whereas pharmacists were more likely to seek such information from electronic references than for general drug information. The findings of this study improved the understanding of where health practitioners usually obtain DDI information; however, little is known about the relative usefulness of these sources and clinicians’ satisfaction with these different sources.

2.4 DDI Alerts

2.4.1 Computerized Prescription Entry and Drug-Drug Interaction

Several studies have found that the use of computerized physician order entry (CPOE)
can be an efficient means for decreasing omission errors (Overhage et al. 1997),
transcription errors (Mekhjian et al. 2002), serious medication errors (Bates et al. 1998),
and injury from ADEs (Raschke et al. 1998). Despite the advances in computer
technology and the touted benefits of CPOE, however, it is not widely used. In 1997,
Ash and colleagues found that 32.1% of 1000 U.S. hospitals surveyed reported complete
or partial availability of CPOE; however, CPOE was not widely and routinely used in
these hospitals (Ash et al. 1998). The authors conducted a similar survey in 2002 which
included 964 randomly selected U.S. hospitals. The survey results indicated that only
9.6% of the hospitals had CPOE completely available while 6.5% reported partial
availability (Ash et al. 2004). The authors believed that the decrease in the availability
could be attributed to the potentially inflated figures reported in 1997 (Ash et al. 2004).

The use of CPOE can substantially reduce medication errors when clinical decision
support features such as drug-disease contraindications and DDI alerts are incorporated
into the system (Evans et al. 1994; Bates et al. 1999; Kuperman et al. 2001; Tamblyn et al.
2003; Galanter et al. 2005). In recent years, efforts have been made to use computer
systems to detect and reduce DDI prescribing and dispensing. A study conducted in
Israel concluded that implementation of CPOE, coupled with DDI screening software in
community-based pharmacies and medical practices, can be effective in preventing
patient exposure to potentially severe DDIs (Halkin et al. 2001). Despite the ability of
computerized alerting systems to reduce DDIs, little is known about the extent to which
the alerts are actually helpful in reducing morbidity and mortality caused by DDIs
(Hansten 2003; Weingart et al. 2003). In addition, numerous deficiencies and
limitations of DDI screening systems in the US have been identified, including an excessive number of drug interactions on the systems, incorrect handling of drug class differences, and inadequate management guidelines (Hansten 2003). A study of 50 pharmacies in the Washington, DC, area found that 29% of pharmacies with computer programs failed to detect a potentially fatal DDI (Cavuto et al. 1996). Similarly, suboptimal performance of community pharmacy drug interaction software was also documented in a study conducted by Hazlet and colleagues (Hazlet et al. 2001). The study results indicated that the software systems failed to detect clinically relevant DDIs one-third of the time and that the sensitivity of the programs ranged from 44% to 88% (Hazlet et al. 2001). The study findings were updated by Abarca et al. in 2004 based on a convenience sample of eight community pharmacies and five hospital pharmacies (Abarca et al. 2006a). The authors concluded that the performance of community pharmacy computer systems in screening DDIs appears to have improved, but significant variation was found in the performance of hospital pharmacy computer systems (Abarca et al. 2006a).

2.4.2 Healthcare Professionals’ Satisfaction with and Attitude toward DDI alerts

Several evaluations of DDI alerts have demonstrated that, in general, healthcare professionals have a positive attitude towards DDI alerts. Sixty-eight percent of hospital pharmacists who responded to a survey believed that the availability of a drug interaction program increased the number of DDIs identified (Elanjian et al. 1993). Among various types of on-line drug utilization review messages, DDI alerts was
reported as the most useful by community pharmacists (Armstrong and Markson 1997). Krall and Sittig surveyed 100 Kaiser Permanente primary care clinicians on the desirability of potential electronic alerts (Krall and Sittig 2001). The authors found that drug related alerts were more highly rated than health maintenance or disease state reminders. Thirty, or 71%, respondents indicated that DDI alerts would always be useful (Krall and Sittig 2001). A general practitioner survey conducted in the UK indicated that 90.4% of respondents agreed that drug interaction alerts were useful in prescribing (Magnus et al. 2002b). In 2000, Glassman and Simon surveyed 263 Veterans Affairs medical center (VAMC) clinicians about automated drug alert system, which included automated alerts for approximately two thousand specified drug combinations of varying severity (Glassman et al. 2002). Overall, most (55%) of respondents felt that DDI alerts improved their ability to prescribe safely whereas only 9% disagreed (Glassman et al. 2002). A follow-up survey was conducted in 2002, which suggested that clinicians generally were very supportive of the drug alert system (Glassman et al. 2006). More recently, Abarca and colleagues surveyed community pharmacy managers to examine pharmacists’ attitude toward computerized DDI alerts (Abarca et al. 2006b). The findings of the study suggested that pharmacy managers generally did not feel that DDI alerts were a waste of time; however, they were not confident in the meaningfulness of the DDI alerts generated by their computer systems (Abarca et al. 2006b). The study results also showed that positive perceptions of DDI alerts were associated with pharmacy software with detailed DDI information and the ability to customize DDI alerts (Abarca et al. 2006b).
Despite healthcare professionals’ general positive attitude towards DDI alerts, one major concern that has been expressed about the use of DDI alerts is their high volume and low clinical significance. Two surveys of clinicians showed that the most commonly reported barriers limiting the use of drug alerts was “poor signal to noise” ratio or too many nonrelevant alerts (Glassman et al. 2002; Glassman et al. 2006). More than half of the community pharmacists surveyed in a recent study believed that more than 70% of the DDI alerts were not clinically significant (Abarca et al. 2006b). Another study conducted in primary care noted a 94.6% override rate with drug interaction alerts and 40.6% of a sample of the alerts were judged invalid by an independent panel of physician reviewers (Weingart et al. 2003). An interview with community pharmacists indicated that the large number of DDI alerts may make pharmacists desensitized to truly important interactions (Murphy et al. 2004). Because too many alerts can cost lots of time and mental energy, “alert fatigue” may occur and may cause important alerts to be ignored or missed (Bates and Leape 1996; Peterson and Bates 2001). Therefore, additional research and efforts are needed to improve the signal-to-noise ratio of DDI alerts.

2.5 Item Response Theory

This section begins with an introduction of IRT. The limitations of CTT will be summarized first, followed by the discussion of the distinctive advantages of IRT over CTT. Several commonly-used IRT models will then be described. Finally, examples of applying IRT analyses to research in health sciences will be provided.


2.5.1 Introduction to Item Response Theory

The act of measurement is an essential component of scientific research. Measurement can be thought of as the process of assigning numbers to the properties of objects according to rules (Crocker and Algina 1986). Unlike physical attributes (e.g., height or weight), psychological attributes, or psychological traits, cannot be measured directly. The science of measuring intangible human traits, or psychometrics, has its roots in education and psychology and has been applied in health measurement for about 30 years (Hobart 2002). The prevailing paradigm in measurement has been the CTT, sometimes referred to as the true score theory. Despite its strengths and long history, there are some limitations inherent in CTT. A major limitation of CTT is that examinee ability is confounded with the difficulty of the test item so the two cannot be estimated separately (Downing 2003). CTT-based item statistics such as item difficulty (i.e., proportion correct) and item discrimination (i.e., point biserial correlations) are dependent on the sample of examinees from which they are obtained, that is, are sample-dependent (Hambleton and Jones 1993). Conversely, test score often used as an indicator of examinee ability is test dependent; that is, an examinee’s test score depends on the particular set of items administered (Hambleton et al. 1991). As a result of sample dependency, it is very difficult to compare items whose characteristics are obtained from different samples of examinees. In addition, different items assessing the same construct cannot be linked to a common metric. Similarly, due to test dependency, it is difficult to compare examinees who take different tests. Another problem with CTT
is that there is only one single standard error of measurement (SEM), which is used to construct confidence intervals for examinees’ test scores. In CTT, SEM can be computed as follows:

\[ \sigma \sqrt{1 - \gamma_{xx}} \]

where \( \gamma_{xx} \) is the estimated reliability of the scale, and \( \sigma \) is the standard deviation of the observed test scores.

This SEM applies to all scores of the examinees taking the test. However, this is an unrealistic simplification because the error tends to be unequal across trait levels; the error is actually smaller in the middle of the scale and larger at the extremes (Streiner and Norman 2003).

Given the limitations of CTT, the development of modern test theory, i.e., IRT, offers an alternative method to determine a scale’s psychometric properties. IRT is essentially a statistical theory consisting of mathematical models that enable predictions of how examinees at different ability levels of an underlying, or latent, trait should respond to a test item (Crocker and Algina 1986). IRT, as its name suggests, yield a more complete picture of how an item functions, whereas CTT models focus more on the test as whole (Chang and Reeve 2005). The main purpose of IRT analysis is to estimate the location of items (i.e., relative difficulty) and examinees (i.e., ability level) on the underlying, continuous trait measured. Because both examinees and items are scaled on the same continuum, items can be optimally selected to provide a good estimate of examinee ability at any level of the scale.

IRT offers a solution to some limitations of CTT. For example, when the assumptions of an IRT model are met and the model can be statistically fitted to the data, examinee
ability is estimated independently of the particular set of items that are administered (i.e., test-free) and item parameters (e.g., item difficulty) are not dependent on the particular sample of examinees taking those items (i.e., sample-free). This theoretical advantage of invariance is one of the most important purported advantages of IRT over CTT and is shared by all IRT models. The invariance properties are obtained because information about the statistical properties of items is taken into account in examinee ability estimation, and information about the ability levels of examinees is taken into account in the estimation of item statistics (Hambleton 2000).

A distinct advantage of IRT over CTT is that the scale that emerges from an IRT analysis, especially in the one-parameter model which will be described shortly, truly has psychometrically-proven interval scale properties (Streiner and Norman 2003). As such, the IRT scale is less likely to violate the assumption of interval scale when applying parametric statistics (Cella and Chang 2000). Another advantage of IRT is that the SEM is estimated for each individual trait level, rather than using a single SEM for all scores as in CTT. This makes IRT more realistic, given the fact that the SEM varies depending on what the examinee’s test score is (Streiner and Norman 2003).

An important practical implication of IRT is computer-adaptive testing (CAT), a measurement approach in which the selection of items is adaptive or tailored for each examinee (Cook et al. 2005). In CAT, after the first mid-difficulty item, presentation of items is determined by examinee’s responses to previous ones so the examinee does not need to answer all the items in a test. Compared to traditional paper-and-pencil tests, CAT provides more precise estimates of examinee ability using fewer test items.
However, challenges of the development of a CAT include high cost, high level of technical expertise, and preparation of large numbers of test items that cover all levels of the construct measured (Cook et al. 2005).

Despite the advantages of using IRT models, there are methodological and practical challenges. For example, IRT is statistically and conceptually more sophisticated than CTT. Without proper knowledge and/or practical experience of applying IRT, it is difficult for newcomers to understand and implement IRT in their test development. Conversely, for researchers who apply IRT in their studies, it is challenging to communicate study results in an easy-to-understand way to those who are not acquainted with IRT. In addition, given the mathematical complexity of IRT, a computer software program is indispensable for IRT analysis. Although there are various IRT software programs available, none of them are particularly user-friendly (Hays et al. 2000). The development of IRT software that is easy to learn and use could facilitate widespread application of IRT (Hays et al. 2000). Another limitation for successful application of IRT is the requirement of a relatively large sample size. In order to have enough power to detect poor model-data-fit, the minimum number of examinees required for the simplest IRT model is approximately 200, and up to 1,000 or more examinees may be needed for more complex models (Downing 2003). On the other hand, however, analysis using large samples may cause model rejection even if the practical consequence of the poor model-data-fit is small (Hambleton 2000).

There are numerous IRT models with different mathematical functions and with various assumptions. An assumption common to most IRT models is the assumption of
unidimensionality, which means that only one latent trait (e.g., ability) is measured by the items that make up the test (Hambleton et al. 1991). If more than one single trait is measured by the test, most IRT models will not fit the data and cannot be used to estimate examinee ability and item characteristics (Downing 2003). There are IRT models that allow multidimensionality; however, the discussion of these models is beyond the scope of this dissertation. Another important assumption is local independence, which asserts that a person’s responses to any pair of items are statistically independent. This assumption holds when the relationships among items (or examinees) is fully characterized by the IRT model (Embretson and Reise 2000).

Commonly used unidimensional IRT models are summarized in Table 2.1. The three most popular IRT models are one-, two-, and three-parameter logistic models. These models can be applied to dichotomously-scored items or items with dichotomous response choices, such as yes/no, right/wrong, and true/false. As suggested by their names, the primary distinction among these models is in the number of parameters that characterize an item’s functioning and thus need to be estimated. The 1-parameter logistic (1-PL) model, also referred to as the Rasch model, focuses on item difficulty as the sole parameter of interest (Cella and Chang 2000). The value of the item difficulty parameter needs to be estimated for each item in the test. Item difficulty indicates the ability/trait level needed for an examinee to have a 50% chance of endorsing an item (i.e., responding “yes” to a yes/no question) or answering the item correctly. In other words, item difficulty refers to the probability of endorsement or correctly answering the item; the greater the value of item difficulty, the lower the probability of the item being
endorsed or answered correctly, thus the more difficult the item. An examinee’s response to an item is a function of the level of the examinee’s ability and the difficulty of the item. The probability of a positive/correct response to an item is dependent on the difference between the difficulty of the item and the ability level of the person on the latent trait:

$$Pi(\theta) = \frac{e^{(\theta - b_i)}}{1 + e^{(\theta - b_i)}} \quad i = 1,2,\ldots n$$

where

- $Pi(\theta)$ is the probability that a randomly chosen examinee with ability $\theta$ answers item $i$ correctly, or endorses item $i$
- $b_i$ is the item $i$ difficulty parameter
- $n$ is the number of items in the test, and
- $e$ is the base of the natural logarithm whose value is 2.718

The Rasch model uses a logistic function to create a common reference scale for examinees and items. The unit of the continuum is called logit (log odds unit). In other words, Rasch analysis converts ordinal level data to interval-level measures with logits as the equal-interval unit.
Table 2.1 Commonly used unidimensional IRT models

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Estimated Parameter</th>
<th>Dichotomous responses</th>
<th>Polytomous Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Parameter</td>
<td>Item difficulty</td>
<td>Rasch model</td>
<td>Rating scale model</td>
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<td></td>
<td></td>
<td></td>
<td>Partial credit model</td>
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<tr>
<td>2-Parameter</td>
<td>Item difficulty and</td>
<td>2-Parameter logistic model</td>
<td>Generalized partial credit model</td>
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<tr>
<td></td>
<td>item discrimination</td>
<td></td>
<td>Graded response model</td>
</tr>
<tr>
<td>3-Parameter</td>
<td>Item difficulty, item discrimination, and guessing parameter</td>
<td>3-Parameter logistic model</td>
<td>None</td>
</tr>
</tbody>
</table>

The 2-parameter logistic (2-PL) model is identical to the 1-PL model except for the presence of two additional elements, i.e., D and ai:

$$P_i(\theta) = \frac{e^{Da_i(\theta-h_i)}}{1 + e^{Da_i(\theta-h_i)}} \quad i = 1, 2, \ldots, n$$

where

- D = 1.7 is a scaling factor that makes the logistic function essentially the same as the normal ogive model.
- ai is the item discrimination parameter for item i.

The higher the value of item discrimination parameter, the better the item discriminates between persons of different trait levels near the inflection point (i.e., item difficulty...
parameter). Highly discriminating items can demarcate fine gradations among examinees with similar levels of the trait being measured, that is, to discriminate among them (Cook et al. 2005). In the 1-PL model, it is assumed that all items are equally discriminating; in other words, the item discrimination parameter, $a$, is fixed at the same value for all items.

The 3-parameter logistic (3-PL) model includes a pseudo-chance (guessing) parameter $c$, as well as item discrimination and difficulty parameters:

$$P_i(\theta) = c_i + \frac{e^{\alpha_i(\theta-b_i)}}{1 + e^{\alpha_i(\theta-b_i)}} \quad i = 1,2,\ldots,n$$

This additional parameter, $c$, accounts for the impact of chance on observed scores, or the probability of answering the item correctly due to chance or guessing. This parameter allows for examinees, even those with low ability, to have a minimal probability $c$ of answering moderate or hard items correctly. In 2-PL model, $c$ is set at zero for all items. The guessing parameter is usually applied to a knowledge-based test where an examinee’s responses are scored as correct or incorrect.

IRT models can be distinguished not only by the number of parameters, but also by the number of response choices in the rating scale (Cella and Chang 2000). Examples of IRT models for items with multiple, ordered response categories (e.g., strongly disagree, disagree, neutral, agree, strongly agree) are provided in Table 2.1. These multiple-category types of items are often highly advantageous because, compared to dichotomously-scored items, they are more reliable and provide more information about examinees (Embretson and Reise 2000). Similar to dichotomous items, the responses to
polytomous items traditionally have been summated and the sum score has been considered the best estimate of the respondent’s score on the construct measured. The rationale behind this summative procedure is CTT, which assumes that all items are parallel, or in other words, all items are assumed to be replications of each other (van Alphen et al. 1994). With CTT, researchers often ignore the fact that the response options in polytomously-scored items rarely have the interval-level properties (i.e., distance between adjacent options is constant across all response options) and assume that the actual ordinal data are “close enough” to the interval level (Streiner and Norman 2003). Polytomous IRT models provide another approach to analyzing polytomous response data, which will be described below.

Many IRT models are available for items with multiple, ordered responses, but only four commonly used ones will be introduced here. The partial credit model (PCM) and rating scale model (RSM) are extensions of the Rasch model (Andrich 1978a; 1978b; Masters 1982). In PCM and RSM, each item is characterized by a series of between-category threshold parameters that define the difficulty of response categories. The number of between-category threshold parameters is equal to one less than the number of response categories. The threshold is the trait level at which a response in a category becomes more likely than a response in the previous category (Hays et al. 2000). For example, for item $i$, if the threshold between “strongly disagree” and “disagree” is $x$, this means that persons at the trait level below $x$ are likely to choose “strongly disagree” while persons at the trait level above $x$ are likely to choose “disagree” or a higher level of the category (i.e., neutral, agree, strongly agree).
scale (i.e., item difficulty) represents the average difficulty for that particular item relative to its category thresholds (Embretson and Reise 2000). Like the 1-PL model, both PCM and RSM assume that all items are equally discriminating. The difference between PCM and RSM is that in RSM the threshold pattern, or the spread of the thresholds, which can be estimated from actual data, is identical across items, whereas in PCM, the spread of the thresholds can differ among the items. For example, if the spread of the thresholds for an item with four response categories (e.g., not at all, a little, quite a bit, very much), and thus three thresholds, is 1.1 and 0.8, this means that the distance between the first two thresholds and the distance between thresholds 2 and 3 is 1.1 and 0.8 logits, respectively. In RSM, all items have the same between-threshold distances (i.e., 1.1 and 0.8 logits in the previous example) although the location of the items on the trait scale may differ, whereas in PCM the distances may vary from item to item.

The graded response model (GRM) and generalized partial credit model (G-PCM) are extensions of the 2-PL model and both models are used when item responses can be characterized as ordered categorical responses (Samejima 1969; Muraki 1992). G-PCM is a generalization of the PCM that includes a slope parameter indicating the degree to which categorical responses vary among items as the trait level changes (Embretson and Reise 2000). Similarly, GRM includes a slope parameter in addition to the item difficulty parameter; the higher the value of the slope parameter, the better the response categories differentiate among trait levels (Embretson and Reise 2000). In GRM, the items in a test need not have the same number of response categories, and computing the conditional probability for an examinee responding in a particular category requires a
two-step process (Embretson and Reise 2000).

When applying IRT, there are many models to choose from, and unfortunately there is no guidebook that tells how the selection should be done (Hambleton 2000). Several criteria have been proposed for model selection, including the desired scale properties for the measure, the fit of the data, and whether the model assumptions are met (Crocker and Algina 1986; Embretson and Reise 2000). There are several goodness-of-fit analyses available for checking model assumptions and the properties of invariance (Hambleton et al. 1991). Using these analyses, researchers can determine the extent to which several IRT models fit their data and choose one for a particular application (Hambleton 2000). Model-data fit is important because, as mentioned previously, the invariance of item and ability parameters does not hold in a poorly-fitting model. Other considerations for model selection include sample size, simplicity, and interpretability. More complex models need a larger sample to obtain stable parameter estimates because there are more item parameters that need to be estimated. For dichotomous items, if both guessing and variation in item discrimination can be negligible, the Rasch model is preferred. Compared to more complex IRT models, the advantages of using the Rasch model include its relative simplicity, ease of interpretation, and requirement of fewer examinees.

2.5.2 Application of Item Response Theory in Health Sciences

Measurement has played an essential role in research in the health sciences as in other scientific disciplines. Throughout the past decade, the use of IRT models in health care has grown considerably, including test validation (Haley et al. 1994; Cella et al. 1996),
test development (Mungas and Reed 2000), test equating (i.e., linking test scores from one test to another) (McHorney and Cohen 2000; Orlando et al. 2000; Badia et al. 2002; McHorney 2002), item banking (Holman et al. 2005; Lai et al. 2005), examining measurement bias (i.e., variations in item functioning due to different group membership) (Teresi et al. 1995; Teresi et al. 2000; Fleishman et al. 2002; Kim et al. 2002), computer adaptive testing (Ware et al. 2000; Haley et al. 2005), and selecting items for minimum item sets needed to provide comparable measurement precision and reliability (Prieto et al. 1998; Mallinson et al. 2004; Hibbard et al. 2005). In this dissertation study, IRT will be used to analyze items assessing prescribers’ knowledge and opinions. Examples of applying IRT to knowledge or opinion assessment in health sciences will be described below.

In the development and validation of a 21-item nutrition test measuring knowledge of the fat content of food-products, Rasch analysis was used to identify items misfitting the model and to examine the unidimensionality of the test (Steenhuis et al. 1996). Specifically, the likelihood-ratio statistic was calculated to examine the model-data fit (Steenhuis et al. 1996). The authors found that the omission of two test items could result in a good model-data fit. In this study, Rasch analysis was only used to provide additional information about the test properties, and the respondents’ nutrition knowledge was indicated by the total number of correctly-answered items rather than by the scores that could have been derived from the Rasch analysis. Similarly, Rasch analysis was performed to evaluate the internal structure of the 18 dichotomously-scored items testing outpatients’ knowledge about randomized clinical trials (RCT) (Kjaergaard et al. 1998).
According to the analysis, in order to keep the unidimensionality of the test, one misfitting item was excluded from score calculation. When the association between outpatients’ RCT knowledge and other variables was examined, the number of correctly-answered items, instead of the IRT-analysis-derived score, was used to indicate the patients’ RCT knowledge.

More recently, in addition to examination of test properties, IRT analysis has been used to estimate examinees’ trait level, such as knowledge of or attitude towards a subject. In a survey of internal medicine residents, Block and colleagues assessed the residents’ knowledge about obesity and attitudes towards the treatment of obesity (Block et al. 2003). The knowledge test items were dichotomously-scored (i.e., either correct or wrong), whereas all attitude items required answers on a 6-point Likert scale ranging from “strongly agree” to “strongly disagree” (Block et al. 2003). A one-parameter IRT analysis was undertaken using WINSTEPS software to estimate summary knowledge and attitude measures for each respondent (Block et al. 2003). Furthermore, the association between knowledge and attitude was examined based on these IRT-analysis-derived summary scores, although the correlation was found to be low and not statistically significant (Block et al. 2003). Similarly, IRT analysis was applied to examine knowledge and attitudes towards asthma in a study evaluating the impact of a pediatric asthma education program (Jackson et al. 2006). Knowledge and attitude data were evaluated via Rasch dichotomous model and rating scale model (RSM), respectively. After removing a misfitting item (i.e., outfit mean-square = 1.35) from the analysis, the remaining seven knowledge items demonstrated unidimensionality and an item reliability,
analogous to a KR-20 or Cronbach’s Alpha, of 0.98 was calculated (Jackson et al. 2006). The authors also presented an item map, which provided a visual representation of the distribution and hierarchical order of student ability and item difficulty. For the 3-point scale attitudinal items, RSM analysis identified two misfitting items (i.e., outfit mean-square = 4.03 and 1.77), which were eliminated from attitude score calculation (Jackson et al. 2006). The respondents’ asthma knowledge and attitudes were estimated with the unit of logits by applying corresponding IRT analysis. In addition, participants’ asthma knowledge and attitudes were evaluated via a pretest-posttest design (i.e., before and after attending the program) and a statistically significant increase in mean logit scores was found on both evaluations (Jackson et al. 2006). In another recent study, when developing survey instruments to evaluate diabetes knowledge and self-efficacy, Gerber and colleagues used IRT analysis to investigate the psychometric properties of the data collected (Gerber et al. 2006). The ten multiple-choice knowledge items were dichotomously-scored, whereas the efficacy items used a Likert-type scale, ranging from 1 indicating “not confident doing what the statement says” to 4 indicating “very confident doing what the statement says” (Gerber et al. 2006). Knowledge and efficacy items were assessed using Rasch dichotomous model and RSM, respectively. The participants’ knowledge and self-efficacy scores obtained from the IRT analyses were used in subsequent analyses correlating the scores with health literacy and hemoglobin A1c level.

IRT has also been used to calibrate medical examinations and provide psychometric information to test developers. The Department of Pediatric Dentistry at Baylor College
of Dentistry, Dallas, Texas, utilized Rasch analysis techniques to carefully select test items for Objective Structured Clinical Examinations that measured students’ competency (Boone et al. 2001). An item map was generated following a Rasch analysis of a 96-item exam administered in the middle of the second-year preclinical course designed to prepare students to enter the clinic. The map provided a visual representation of test items appearing easier or more difficult than anticipated, which had implications for curriculum design and the preparation of subsequent examinations. For example, in the case of items that appeared more difficult to students than originally anticipated by the authors, the map helped identify these items that students had not mastered; such sub-competency needed to be re-taught and retested before moving on in that component of the curriculum (Boone et al. 2001). Therefore, the Rasch analysis results were helpful for curricular adjustments and examination refinement (Boone et al. 2001). Bhakta and colleagues used Rasch analysis to examine the results from the extended matching question (EMQ) examination (i.e., a form of multiple-choice type question designed to test students’ knowledge) taken by 4th year undergraduate medical students in 2001 (Bhakta et al. 2005). The exam consisted of 98 EMQs distributed across eight specialties and all responses were dichotomously coded: either correct or incorrect. Analysis results demonstrated internal construct validity and the absence of bias on the majority of test items (Bhakta et al. 2005). Specifically, after omitting three misfitting items (fit criteria not reported), the overall fit of the remaining 95 EMQs to the Rasch model improved and showed no significant item–trait interaction. The item map indicated that the items from each of the component specialties had a reasonable spread
of difficulty across the logit scale (Bhakta et al. 2005). Several dental and medical agencies also have used the Rasch model for board certification and/or recertification (e.g., Council on Certification of Nurse Anesthetists, American Dental Association, American Board of Pediatric Dentistry, American Society of Clinical Pathologists, and American Board of Medical Examiners) (Zaglaniczny and Healey 1998; Boone et al. 2001).

IRT analysis has been used to evaluate tests assessing attitudes in health science research. Because most attitude tests consist of items with multiple, ordered responses, polytomous IRT models are employed to evaluate these tests. In addition to examples described previously, several satisfaction scales were developed and evaluated using IRT analysis, as described below. Hernandez and colleagues developed a seven-item test in both English and Spanish to assess patients' satisfaction with pharmacists (Hernandez et al. 2000). The unidimensionality and construct validity of these seven 5-point Likert scale-type items were analyzed with the RSM. The study results suggested that none of the items in either language was a misfit (i.e., outfit mean-square values outside 0.7-1.3), which indicated their ability to measure a unidimensional construct (Hernandez et al. 2000). In addition, based on the item difficulty parameters calculated by the IRT analysis, the difficulty hierarchy for the items was the same in the two languages, indicating the items performed identically in both versions (Hernandez et al. 2000). Morales et al. used the G-PCM, a 2-PL polytomous IRT model, to investigate nine satisfaction-with-medical-care items with a 7-point response format (the best, excellent, very good, good, fair, poor, very poor) (Morales et al. 2000). IRT analysis results
identified two items that had statistically significant differential item functioning (DIF) between whites and Hispanics. Because the difference between satisfaction scores for whites and Hispanics was similar whether or not these two items were included, it was concluded that the differences in mean satisfaction scores between the two groups should be viewed as arising from actual differences in experiences with care, rather than due to measurement bias (Morales et al. 2000). More recently, Scholle et al. reported the development and psychometric properties of a new survey instrument that was designed to measure women’s satisfaction with their primary care services (Scholle et al. 2004). During item elimination and selection process, all 5-point items (1 = not at all satisfied; 2 = somewhat satisfied; 3 = satisfied; 4 = very satisfied; and 5 = extremely satisfied) were assessed by fitting the GRM (Scholle et al. 2004). Based on the item discrimination parameters calculated by the IRT analysis, the authors were able to identify items with a better discriminating ability (i.e., the items that better differentiate respondents among the levels of satisfaction).

In summary, based on the studies reviewed above, in health science research, knowledge tests usually consist of dichotomously-scored items. Partial credits, which are commonly used in the scoring of written essays, are rarely used in knowledge tests in health science research. Rasch dichotomous model has been the most popularly employed IRT method in the assessment of knowledge test data. Health science researchers either used IRT analysis alone or, in most cases, in combination with CTT analysis to evaluate the psychometric properties of the test developed. The researchers who applied IRT analysis in their studies viewed IRT analysis as a tool that has several
advantages over CTT and produces additional information about the test properties. For attitude tests consisting of items with multiple, ordered responses, RSM was more commonly used than PCM and 2-PL models, which might be due to the smaller sample size required for RSM. The two aforementioned studies that used 2-PL polytomous IRT model both had more than 1,000 respondents in the study sample, with one study including about 7,000 survey respondents (Morales et al. 2000; Scholle et al. 2004). Given the common use of psychological measurement in health sciences and the ability of IRT to address a few limitations inherent in CTT, health science researchers need to familiarize themselves with and consider applying IRT to test development, refinement, and analysis.
CHAPTER 3

METHODS

3.1 Research Design

The primary objective of this study was to assess whether prescribers could recognize clinically significant interacting drug combinations. The drug pairs were selected from a list of 25 clinically important DDIs that was developed by an expert panel through a modified Delphi consensus-building process (Malone et al. 2004). Also, this study was conducted to examine the usefulness of various sources that prescribers usually go to for DDI information. The study was a cross-sectional mail survey using a matched cohort study design. A survey questionnaire was developed to collect the information about prescribers’ demographic and practice characteristics and their usual source of DDI information. The questionnaire also included a 15-item knowledge test of DDIs. Data was collected by mailing the survey packet to the two cohorts of prescribers. One cohort consisted of prescribers that had written at least one prescription for a DDI (i.e., case cohort), whereas the other cohort consisted of prescribers that had no recent history of DDI prescribing (i.e., control cohort). Prescription claims data from a PBM company were used to select prescribers for both cohorts. The distribution of the mail surveys followed a modified Total Design Method approach (Dillman 2000).

The survey was conducted using a self-administered mail questionnaire. Compared to alternative methods (e.g., telephone and face-to-face interviews), the advantages of mail survey include obtaining a large sample with relatively low cost, feasibility of
coordinating a national or international survey from one central office, and minimized interviewer bias and social desirability bias (Dillman 1978; Streiner and Norman 2003). The major drawbacks of this method include relatively low response rate, lack of information about non-respondents, higher likelihood of item omission, delayed response, and limited flexibility of question construction (Dillman 1978; Streiner and Norman 2003). A mail survey approach was chosen because it was considered the most economical and feasible method to reach a large sample with a wide geographic distribution. In addition, the self-administration and anonymity properties of the survey may avoid embarrassment when assessing prescribers’ knowledge of DDIs. If a telephone or face-to-face interview had been adopted, prescribers who felt insecure about their DDI knowledge could have felt pressured and found the interview intimidating; thus they may have been more likely to refuse to participate. Moreover, given the busy schedule a prescriber usually has, self-administration provides the opportunity for prescribers to complete the questionnaire at their convenience. In order to enhance response rate and avoid delayed response, efforts were made during the development and distribution of survey instruments, which will be described in the following sections.

After the data were collected, IRT was applied to the evaluation of the test of prescribers’ ability to recognize clinically significant DDIs. Because these knowledge test items were dichotomously-coded, IRT models for dichotomous data were used for knowledge data. IRT was also used to analyze the attitude assessment items in the questionnaire. Because these items were in a 5-point response format, IRT models for polytomous data were used for attitudinal data.
3.2 Survey Instruments

A survey questionnaire specific to the study was developed by the Arizona Centers for Education and Research on Therapeutics (AzCERT) research group. The research group included PhDs and PharmDs who had extensive research experience and publications on DDIs as well as clinical training in pharmacy and advance practice nursing. The survey was directed to prescribers and asked their opinions about DDIs and computerized DDI alerts, their practice characteristics (e.g., specialty, patient workload, type of practice site, prescribing method, type of provider, years in practice, use of electronic medical record), and their source of DDI information; the survey also included a knowledge test of DDIs. The questionnaire contained original questions developed specific to the objectives of this study and questions from previously published research on DDIs and computerized DDI alerts (Glassman et al. 2002; Magnus et al. 2002a).

The items assessing prescribers’ knowledge of DDIs were selected from the clinically important DDI list developed by Malone and colleagues (Malone et al. 2004). The list consisted of 25 DDIs that are likely to be encountered in community and ambulatory pharmacy settings and are detectable by computerized pharmacy systems. The 25 DDI pairs can be divided into four groups, as displayed in Table 3.1.
Table 3.1 Drug-drug interactions with clinical importance

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<th>DDIs involving MAOIs</th>
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<th>DDIs involving anticoagulants</th>
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<td>Anticoagulants</td>
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<td>Warfarin</td>
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<th>DDIs involving anti-infectives, antibiotics, and antifungals</th>
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<td>Azole antifungals</td>
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<td>Azole antifungals</td>
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<tr>
<td>Clarithromycin</td>
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<tr>
<td>Macrolide antibiotics</td>
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<td>Macrolide antibiotics</td>
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<tr>
<td>Quinolones</td>
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<td>Rifampin</td>
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<td>Rifamycin</td>
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<td>Trimethoprim</td>
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<td>Zidovudine</td>
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<tr>
<th>Miscellaneous DDIs</th>
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<tr>
<td>Carbamazepine</td>
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<td>Nitrates</td>
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<td>Theophyllines</td>
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<td>Thiopurines</td>
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MAOIs = Monoamine Oxidase Inhibitors.
NSAIDs = non-steroidal anti-inflammatory drugs.
SSRIs = selective serotonin reuptake inhibitors.
The DDI list was developed through a three-stage process: (1) candidate DDIs were first selected from a review of four well-known drug interaction compendia, (2) a systematic literature review was conducted and an evidence report for each candidate DDI was developed, then (3) these evidence reports were reviewed and systematically evaluated through a modified Delphi process by an expert panel that consisted of two physicians, two clinical pharmacists, and an expert on DDIs (Malone et al. 2004). As indicated by a study of a drug claims database of a PBM company, the prevalence of the 25 DDIs of interest varied considerably from 0.08 to 279 per 100,000 persons (Malone et al. 2005). The three medication pairs with the highest prevalence were warfarin and nonsteroidal anti-inflammatory drug (NSAID), azole antifungal and benzodiazepine, and anticoagulant and thyroid hormone (Malone et al. 2005).

The survey questionnaire also contained questions about prescribers’ usual source of DDI information. One question asked prescribers what reference/person they used first when they wanted to learn more about a drug interaction. Another question asked prescribers who usually informed them when one of their patients was about to be exposed to a potential drug interaction. In addition, several items were developed to assess the usefulness of these various information sources as perceived by prescribers.

The questionnaire was pilot tested to identify problems with comprehension, item response, and time to complete the questionnaire during May 2005 among a random sample of 200 licensed physicians and nurse practitioners in Arizona. A response rate of 12.8% was obtained from the pilot mail survey. The following changes to the questionnaire were made based on the results of the pilot test. In order to more
precisely estimate prescribers’ ability to recognize DDIs, the test items needed to target well on the prescribers’ knowledge level. Based on the responses of the limited number of pilot test respondents, the DDI knowledge items seemed too difficult for them, with the correct response rate below 50% for three-fourths of the items. As such, in the revised version of the questionnaire, several extremely difficult and mid-difficult items were replaced by a few easy items, as determined by an AzCERT researcher with a Pharm.D. degree.

After the pilot test, one concern with the questionnaire was the overall length given that the average time to completion was 12 minutes. In order to address this issue and also preserve the questions related to computerized DDI alerts, two versions of the survey questionnaire were developed: a short and a long version. Both versions were designed to take no more than ten minutes to complete, with the short version being very brief.

The final version of the short survey (shown in Appendix A) contained 16 items about demographics, practice characteristics, workload, and a 15-item DDI knowledge test that asked prescribers to categorize drug pairs based on whether they were DDIs or not. The 15-item DDI test contained 14 standard items and an additional item that was tailored to each individual prescriber based on whether they had prescribed that particular DDI for cases or one of the medications involved in the interacting drug pair for controls. Prescribers were asked to classify each drug pairs as “contraindicated”, “may be used together but with monitoring”, or “no interaction”. A response option of “not sure” was also provided. The long version (shown in Appendix B) contained the same items plus an additional 16 items asking prescribers about their opinions concerning computerized
DDI alerts and prescribers’ usual source of DDI information. Opinions were obtained using a 5-item response scale from ‘1’ (strongly disagree) to ‘5’ (strongly agree) or ‘1’ (never) to ‘5’ (always).

3.3 Sampling

3.3.1 Sample Size Calculation

The principal research purpose of conducting the survey, although not addressed in this dissertation, was to examine prescriber factors (e.g., personal characteristics and practice setting characteristics) that were associated with prescribing a DDI. This research purpose served as the basis for sample size calculation for the survey.

In the US, with claim databases analyses, the rate of serious DDIs in the ambulatory care setting has been estimated to be 0.8% to 2.3% (Solberg et al. 2004; Malone et al. 2005). A conservative rate of 1.5% of DDIs was assumed to be captured by the claim database used in this study. Applying the sample size calculation formula for logistic regression and assuming an alpha error of 0.05, a beta error of 0.20, and a difference of 0.6% in the DDI rates for the binary independent variable of interest, the required sample was calculated to be 3,584 (Hsieh et al. 1998). After further assuming a variance inflation rate factor of 0.8 that adjusted for the effects of covariates in the multiple logistic regression model, the required sample size was around 4,500 (Hsieh et al. 1998). Based on a minimum response rate of 45%, the sample size required was 10,000. Because of the wide variation in the response rates reported in recent national surveys of physicians (Alexander et al. 2005; Audet et al. 2006; Cowan et al. 2006; Vernacchio et al. ...
2006), a value of 45%, a value near the middle of the range, was assumed. Finally, in order to account for potential returned mails, a total of 11,000 prescribers were selected in the survey sample.

For testing the primary research hypothesis, it was assumed that there was an equal standard deviation of 1 logit for the IRT-derived knowledge test scores in both case and control groups, a 1:1 ratio of cases to controls, and a two-tailed test of significance with an alpha of 0.05 and a power of 0.80, a total of 786 prescribers was required to detect a difference in mean knowledge test scores of 0.2 logit, or a conservatively estimated small effect size (Cohen’s $d = 0.2$). Under the same assumptions, if a power of 0.9 was desired, 1,052 prescribers would be required.

The number of examinees needed to estimate IRT model parameters depends on many factors, such as how discriminating the items are and how many item parameters are being estimated (Embretson and Reise 2000). To obtain a precise estimate of item parameters and examinee ability, it is more important to have items targeting examinees on the continuum (i.e., the difficulty of items is similar to the ability of examinees) than to have a large number of items or examinees. That said, to work properly, IRT models require fairly large samples of examinees. As mentioned previously, the minimum number of examinees required to properly test the model-date-fit of the simplest IRT model (i.e., the one-parameter model) is approximately 200. As model complexity increases (i.e. when more item parameters are being estimated), a greater number of subjects will be required (Downing 2003).
3.3.2 Sample Selection

This study adopted a random sample design stratified by the frequency of DDI occurrences. Data from a PBM company covering over 50 million lives nationwide was used to identify prescribers eligible for selection. Prescription claims between January and May 2005 were evaluated to select prescribers for both case and control groups, which prescribers would be candidates for the case and control cohorts in the survey. Specifically, prescribers were included in the case group if they had written at least one prescription that caused an interacting drug combination that was on the 25-DDI list developed by Malone and his colleagues (Malone et al. 2004). In cases where the prescriber had prescribed more than one interacting drug combination, the least frequently occurring combination in the claim database was selected and linked to that prescriber. Thus, prescribers in the case group were only linked to one DDI. Each DDI was linked to a different number of cases; the more frequent the occurrence of the DDI, the more cases in that DDI group. In order to maximize the number of infrequent DDIs and prevent oversampling of frequent DDIs, a multi-stage approach was used to select a sample from the case group. All the prescribers who were linked to a DDI that had fewer than 600 prescribers in the group were selected. A random sample of prescribers was selected from the cases linked to frequently-occurring DDIs (i.e., DDIs that had more than 600 prescribers in the group) to attain a sample of 5500 prescribers in the case cohort. Then the prescribers in the case cohort were matched on a one-to-one basis to select a control cohort (i.e., a group of prescribers that had written a prescription for either one of the medications in the drug combination). The matching was also done
based on the state where the individual practiced, type of provider (i.e., physician or nurse practitioner/physician assistant), and prescription volume.

Following the above-mentioned selection procedures, a total of 11,000 prescribers were selected, with 5,500 in each cohort. Addresses of the prescribers in both cohorts were identified using the Drug Enforcement Agency (DEA) identifier database and verified using the U.S. Postal Service (USPS) national change of address (NCOA) and the coding accuracy support system (CASS) certification process. The DEA number, which is to be solely used for tracking controlled substances, is often used as a general “prescriber” number as a unique identifier for anyone who is authorized to prescribe medication. NCOA corrects address lists electronically by identifying individuals and businesses that have moved within the last three years. The NCOA database contains about 110,000,000 address changes and is updated biweekly. The CASS is a service offered by the USPS to improve the accuracy of the address information in the mailing list. It checks the accuracy of the delivery point codes, ZIP+4 Codes, 5-Digit ZIP Codes and carrier route codes.

During the selection process, particular attention was focused on excluding geographic areas that were affected by the Hurricane Katrina because we would be surveying in Fall 2005 and we did not anticipate responses from these areas (e.g., coastal areas in Louisiana, Mississippi, and Alabama). Because of the low response rate obtained from the national sample, in January 2006 the AzCERT research group decided to conduct a second round of surveying with Arizona prescribers to supplement the data collected from the national survey. The same procedures were followed to identify cases and
controls for the Arizona survey. Prescribers that had been selected for the national survey were excluded from the Arizona sample. A total of 1,500 prescribers were selected and were evenly distributed between the case and control cohorts. Because the survey was focused on Arizona, prescribers who were linked to a DDI were matched to controls based on only prescription volume and type of provider (i.e., physician or nurse practitioner/physician assistant). Minor changes were made to the questionnaire for the Arizona sample (see Appendix C). The Arizona survey questionnaire was identical to the long version of the national survey questionnaire except an addition of eight items assessing satisfaction with computerized DDI alerts for prescribers using CPOE. In addition, the items were re-numbered and re-ordered to facilitate the completion of the questionnaire.

3.3.3 Inclusion Criteria

A prescriber was eligible for selection if he/she (1) prescribed at least one drug involved in the 25 DDIs and a claim for the prescription was submitted by a pharmacy between January and May 2005, and (2) had a DEA number for provider types of physicians or nurse practitioners (NPs) / PAs.

3.3.4 Exclusion Criteria

Prescribers were excluded if their addresses listed in the DEA database did not pass the verification of the NCOA or CASS certification process.
3.4 Ethics

Both national and Arizona survey questionnaires and the cover letters were approved by the institutional review board (IRB) of the Human Subjects Protection Program at the University of Arizona. The entire study was carried out in accordance to the policies and procedures of the IRB. It was made clear in the cover letter that participation was voluntary, withdrawal from the study was allowed at any time, and complete confidentiality of the responses was assured (see Appendices D and E). Responses to the survey were not anonymous, but no prescriber names were linked to the survey questionnaires and no personal identifiers of the prescriber were included in the data. Consent to participate was implied by returning the survey questionnaire. As an incentive to participate, respondents were entered into a drawing to win one of several personal digital assistants with drug information software. The incentive for those responding to the long survey had a greater value than that for those responding to the short survey because of the extra effort required to complete the long survey.

3.5 Data collection

A postal survey was used to collect information from prescribers concerning their practice characteristics and DDIs. In an attempt to obtain a high response rate, distribution of the mail surveys followed a modified Total Design Method approach (Dillman 2000). Previous studies that used Dillman's method were successful in securing high response rates (Anema and Brown 1995). For the national survey, an announcement postcard providing a brief explanation of the study and alerting the
prescriber to the survey was sent out nationwide to the 11,000 prescribers sampled on October 21, 2005. All correspondence was addressed to the prescriber. One week later a survey packet was sent out. The survey packet contained a cover letter that explained the purpose of the study and contained the essential elements of informed consent (see Appendix D), a copy of the survey questionnaire, and the instructions for returning the questionnaire. The cover letter also highlighted the importance of the study and that of the response from the prescribers. Among the 11,000 prescribers, 10% were randomly selected to receive the long version of the questionnaire and the others were sent the short version. Two weeks later a reminder postcard was sent encouraging participation in the study. Another two weeks later a reminder letter (see Appendix E) was sent along with another copy of the survey questionnaire. Data from the returned questionnaires that were received before January 31, 2006 were entered.

Because of the low response rate obtained from the national sample, the AzCERT research group decided to conduct a second round of surveying with Arizona prescribers. The survey mailing was conducted in a similar manner to the national survey. An announcement postcard was sent on February 21, 2006. One week later, a survey packet was sent to prescribers which included the Arizona version of the questionnaire and a business reply envelope. The following week a reminder postcard was sent. Finally, three weeks later a reminder letter was sent along with another copy of the questionnaire.

3.6 Data Entry and Management

Two research assistants from the AzCERT research group entered the data from the
returned questionnaires into Microsoft Access independently. All responses to the choice-type of items were coded with numbers. Although it was clearly stated in the questionnaire that the respondent should select the single best answer to each choice-type of question, there were still multiple selections provided by a few of the respondents. In cases of multiple selections, the random number function in Microsoft Excel was used to randomly select an answer to be entered in the dataset. For the items regarding the prescriber’s specialty area and the description of his/her national board certification, the handwritten answers were entered in the dataset word-by-word. For items number 4 to number 6 (i.e., patients seen per day, work hours per week, and practicing years), if the handwritten answers contained a range, instead of a single number, the middle value of the range was entered. Rounding was conducted when necessary. The coding scheme for DDI knowledge questions was first entering the prescriber’s choice (i.e., 1 = contraindicated, 2 = used with monitoring, 3 = no interactions, 4 = not sure); then the coding was transformed to a value of “1” or “0” depending on whether the choice was correct (i.e., 0 = incorrect, 1 = correct). Correlation analyses were run to identify discrepancies between the two datasets; then the two data enterers reviewed the returned questionnaires together to correct the errors/discrepancies in the datasets.

A response rate was calculated for the national survey and the Arizona survey separately and combinedly. The response rate was calculated by dividing the number of returned questionnaires by the number of returned mails subtracted from the number of mailed questionnaires.
3.7 Statistical Analyses

A returned questionnaire was considered completed if (1) the item of the DDI pair of interest (i.e., the drug pair by which cases and controls was matched) was answered and (2) at least 50% of the DDI knowledge items (i.e., seven of fourteen items) were answered. For the Arizona survey and the long version of the national survey, to be considered completed, additional requirements needed to be met: (1) the item regarding the prescriber’s usual source of DDI information (i.e., question number 14) was answered, and (2) 80% of the items assessing the usefulness of the DDI information source (i.e., four of five items) were answered. Only those completed questionnaires were included in the analyses. The response rate adjusted for the incomplete questionnaires was calculated by dividing the number of completed questionnaires by the number of returned mails subtracted from the number of mailed questionnaires.

In order to increase the statistical power in hypothesis testing, responses from the national and Arizona surveys were combined in the analyses. Analyses were performed using SPSS 14.0 for Windows (SPSS, Inc.), WINSTEPS version 3.57 (Winsteps), and BILOG-MG 3 (Scientific Software International, Inc.). Unless otherwise indicated, statistical significance was set at two-sided \( p \)-value less than 0.05. The analysis plan is detailed below.

Univariate summary statistics were calculated for the demographic and practice characteristic variables as well as the items assessing prescribers’ general opinions about DDIs. For presentation purposes, variables with few responses to some questions were collapsed into fewer categories when necessary. Frequency distributions and means
were used to describe categorical and continuous variables, respectively. The percentages of prescribers using different sources of DDI information are reported. Also, the mean and standard deviation of prescribers’ rating score for each statement about computerized DDI alerts will be presented.

For the DDI knowledge test, the percentage of prescribers choosing each response category and the percentage of correct responses are reported for each item. In addition, data were evaluated via dichotomous IRT analysis. Specifically, the 1-PL, 2-PL, and 3-PL were fitted to the data from the DDI knowledge items. The reason for fitting the data to the 2-PL and 3-PL models was because the guessing parameter is usually applied to a knowledge-based test. Also, it was unknown whether all items are equally discriminating so the 1-PL model may not be sufficient to fit the data. The best fitting model was determined by the marginal log-likelihood statistics, which is a commonly-used model-data fit analysis. When the difference between the models is not statistically significant based on the chi-squared test, the model with the fewer parameters was selected as the best-fitting model for parsimony purpose. Using the best fitting model, the misfitting items (i.e., items that may not contribute to the single trait measured) were removed based on item fit statistics. The item parameters from the best-fitting model were estimated and a DDI knowledge score and its associated standard error were estimated for each respondent. Univariate summary statistics were then calculated for the respondents’ knowledge scores.

For the items assessing the usefulness of DDI information sources, the percentage of prescribers choosing each response category is reported for each item. The data were
assessed using one-parameter IRT models for the polytomous type of data. Specifically, either RSM or PCM will be selected as the best-fitting model for the information source items. Because these items were not included in the short version of the national survey questionnaire, fewer respondents answered these items than those who answered the DDI knowledge items. In view of the limited sample size, it was not considered appropriate to use more complicated models for which more item parameters need to be estimated (e.g., G-PCM and GRM). The RSM will be selected first if it fits the data. If a poor-fit is observed, two approaches will be used to improve the fit: (1) combining the adjacent response categories (e.g., combining “strongly disagree” and “disagree” into one category “disagree”) or (2) using PCM to replace the RSM. If, by visual inspection, the threshold pattern observed in the RSM seem to differ across the items, PCM is likely to provide a better fit to the data. Using the model that best fits the data, misfitting items will be removed. Two fit statistics provided by WINSTEPS can be used to identify misfitting items or examinees: infit mean-square (MNSQ) and outfit MNSQ, which have a range from zero to positive infinity. An infit or outfit MNSQ value of $1 + x$ indicates $(100 \times x)$% more variation between the observed and the model-predicted patterns than would be expected if the data and model perfectly fitted (Bond and Fox 2001). For example, an infit MNSQ value of 1.3 indicates 30% more variation in the observed data than the model predicted and a value of 0.78 indicates 22% less variation in the observed data than what was modeled (Bond and Fox 2001). While the infit statistic is more sensitive to unexpected patterns of responses to items targeted on the examinee’s trait level, the outfit statistic is more sensitive to unexpected patterns of responses to items far
from the examinee’s trait level. The fit criteria for this study are: infit MNSQ $\leq 1.5$
and outfit MNSQ $\leq 2.0$. After the removal of misfitting items, the item parameter
estimates from the best-fitting model will be reported and a score indicating the
usefulness of the DDI information source as perceived by the respondent will be
estimated for each respondent. In addition, two reliability indices provided by the
WINSTEPS software will be reported: item reliability and person reliability index. Item
reliability index indicates the replicability of item placements along the continuum if the
items were to be administered to another sample of examinees with comparable ability
levels. Person reliability index indicates the replicability of examinee ordering that can
be expected if the current sample of examinees were given another set of items
addressing the construct of interest.

The null hypotheses to be tested in this study and the corresponding statistical analysis
are listed below:

$H_01$: There is no difference in DDI knowledge between prescribers who had prescribed
at least one interacting drug combination and prescribers who had no recent
history of DDI prescribing.

Statistical analysis: First, a two-sample t-test was used to compare the mean IRT-derived
DDI knowledge scores of the case and control cohorts. Then a multiple linear
regression model was developed to examine the association between the knowledge
scores and prescribers’ history of DDI prescribing while controlling for potential
confounders. Multiple regression analysis permitted an evaluation of the relationship
between each independent variable and a continuous variable, namely, the IRT-derived
DDI knowledge score, while the influences of other independent variables were adjusted for. The following variables were examined as potential predictors of prescribers’ DDI knowledge test scores: gender, prescription volume, provider type, specialty area, workload (patients seen per day, hours seeing patients per week), primary practice site, years of being a practicing licensed prescriber, history of DDI prescribing, method for prescribing medications, use of electronic medical records, the extent to which the risk for a DDI affects the prescriber’s drug selection, and whether the prescriber has seen a patient who had a drug interaction. The two-way interaction terms included in the model were provider type with primary practice site. Because of the exploratory nature of the current study and the lack of information about the factors relating to prescribers’ DDI knowledge in the literature, the selection of the independent variables and the interaction terms was determined by expert opinions of the AzCERT research group.

Ho2: The prescribers who had prescribed at least one interacting drug combination were equally likely to answer the DDI of interest question correctly as the prescribers who had no recent history of prescribing such an interacting drug combination.

Statistical analysis: A logistic regression model was developed to examine whether the likelihood of correctly answering the DDI of interest question differs between cases and controls while controlling for potential confounders.

Ho3: There is no difference in DDI knowledge among prescribers who usually consult written, electronic, or personal information source for DDI information.
Statistical analysis: The relationship between prescriber’s DDI knowledge and use of DDI information source will be examined using ANOVA. If a significant omnibus F is obtained, the mean knowledge scores of different source groups will be compared pairwise using the Scheffe test.

$H_0$: There is no difference among prescribers’ perceptions of the usefulness of pharmacists, computerized alert systems, PDAs, or other DDI information sources.

Statistical analysis: One-way analysis of variance (ANOVA) will be used to compare the mean usefulness score as derived from the IRT analysis among different sources of DDI information. If the omnibus F is significant, the Scheffe test, a conservative experimentwise alpha error-controlled post-hoc test, will be conducted to make multiple pairwise comparisons among the group means.
CHAPTER 4
RESULTS

4.1 Response Rate

The survey packet was sent to a total of 12,500 prescribers (national: 11,000; Arizona: 1,500). After discarding 402 undeliverable surveys, a total of 1,015 responses were received (national: 739; Arizona: 276), yielding an overall response rate of 8.4% (national: 6.9%; Arizona: 20.0%). Sixty-five questionnaires were deemed incomplete as determined by the requirements mentioned previously. Data from the remaining 950 respondents were included in the analyses, with 695 and 255 respondents coming from the national and Arizona samples, respectively. An overall adjusted response rate was 7.9%, reflecting a national response rate of 6.5% and a response rate of 18.5% for Arizona. The short and long versions of the survey distributed nationally had comparable response rates: 6.5% and 6.3%, respectively.

4.2 Descriptive Statistics

Given the low response rate, it was imperative that the respondents be assessed for representativeness. A comparison between respondents and non-respondents indicated that the two groups had a similar proportion of cases and controls \( p = 0.38 \), and the mean prescription volumes were not statistically different \( p = 0.06 \). However, it was found that the respondent group had a higher proportion of NPs / PAs and prescribers practicing in the Western region of the US than those who did not respond \( p < 0.05 \).
Table 4.1 provides descriptive statistics for the two samples separately and combined. For the national sample, 84.2% were male, 96.3% were physicians, and 87.6% reported having national board certification. The respondents reported being a licensed prescriber for an average (± SD) of 25.2 ± 10.1 years, saw 31.7 ± 30.2 patients per day, and spent 38.1 ± 16.2 hours per week seeing patients. With respect to the practice characteristics of the national sample, approximately half (49.4%) of the respondents reported office-based group practice as their primary practice site, another one-third (35.8%) primarily practiced in office-based solo practice, 71.1% practiced in only one location, 78.4% did not use electronic medical records at their primary practice site, 59.7% provided care for patients outside their usual panel when on-call, and the majority (82.6%) of the respondents most commonly used hand-written prescription order for prescribing medications.

The demographic and practice characteristics of the Arizona sample were similar to those of the national sample, with a few exceptions. As shown in Table 4.1, there were five significant differences between the two samples. Specifically, compared to the national respondents, the Arizona respondents were more likely to be female prescribers ($p < 0.001$), more likely to be nurse practitioners or physician assistants ($p < 0.001$), family physicians or cardiologists ($p < 0.001$), and practiced in office-based group practices ($p = 0.001$). In addition, national respondents were more experienced in prescribing medicines than Arizona respondents, with approximately a mean difference of five years ($p < 0.001$).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>National n (%)*</th>
<th>Arizona n (%)*</th>
<th>Overall n (%)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 695)</td>
<td>(N = 255)</td>
<td>(N = 950)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Male</td>
<td>585 (84.2)</td>
<td>181 (71.0)</td>
<td>766 (80.6)</td>
<td>&lt; 0.001</td>
</tr>
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<td>108 (15.5)</td>
<td>74 (29.0)</td>
<td>182 (19.2)</td>
<td></td>
</tr>
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<td>0 (0.0)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
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<td><strong>Profession</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>669 (96.3)</td>
<td>209 (82.0)</td>
<td>878 (92.4)</td>
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</tr>
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<td>Nurse Practitioner</td>
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<td>25 (9.8)</td>
<td>33 (3.5)</td>
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<td>18 (7.1)</td>
<td>23 (2.4)</td>
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</tr>
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</tr>
<tr>
<td>Other</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>206 (29.6)</td>
<td>106 (41.6)</td>
<td>312 (32.8)</td>
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</tr>
<tr>
<td>Internal Medicine (other than cardiology)</td>
<td>216 (31.1)</td>
<td>79 (31.0)</td>
<td>295 (31.1)</td>
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<tr>
<td>Psychiatry and Neurology</td>
<td>59 (8.5)</td>
<td>13 (5.1)</td>
<td>72 (7.6)</td>
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<td>Cardiology</td>
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<td>24 (9.4)</td>
<td>59 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>34 (4.9)</td>
<td>2 (0.8)</td>
<td>36 (3.8)</td>
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<tr>
<td>Obstetrics and Gynecology</td>
<td>28 (4.0)</td>
<td>5 (2.0)</td>
<td>33 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>24 (3.5)</td>
<td>5 (2.0)</td>
<td>29 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>19 (2.7)</td>
<td>8 (3.1)</td>
<td>27 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>71 (10.2)</td>
<td>11 (4.3)</td>
<td>82 (8.6)</td>
<td></td>
</tr>
<tr>
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<td>2 (0.8)</td>
<td>5 (0.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>National board certification</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>609 (87.6)</td>
<td>222 (87.1)</td>
<td>831 (87.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>83 (11.9)</td>
<td>33 (12.9)</td>
<td>116 (12.2)</td>
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</tr>
<tr>
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<td>3 (0.3)</td>
<td>0.69</td>
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<td><strong>Primary practice site</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Office-based practice (solo)</td>
<td>249 (35.8)</td>
<td>80 (31.4)</td>
<td>329 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Office-based practice (group)</td>
<td>343 (49.4)</td>
<td>134 (52.5)</td>
<td>477 (50.2)</td>
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<tr>
<td>Hospital-based clinic</td>
<td>50 (7.2)</td>
<td>7 (2.7)</td>
<td>57 (6.0)</td>
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<td>Hospital acute care</td>
<td>23 (3.3)</td>
<td>8 (3.1)</td>
<td>31 (3.3)</td>
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<td>7 (2.7)</td>
<td>15 (1.6)</td>
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<td>1 (0.4)</td>
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Table 4.1 Prescribers’ self-reported demographic and practice characteristics (cont.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>National n (%)* (N = 695)</th>
<th>Arizona n (%)* (N = 255)</th>
<th>Overall n (%)* (N = 950)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>When on-call, provide care for patients outside usual panel of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>415 (59.7)</td>
<td>141 (55.3)</td>
<td>556 (58.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181 (26.0)</td>
<td>74 (29.0)</td>
<td>255 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>92 (13.2)</td>
<td>39 (15.3)</td>
<td>131 (13.8)</td>
<td>0.41</td>
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<tr>
<td>Missing</td>
<td>7 (1.0)</td>
<td>1 (0.4)</td>
<td>8 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Practice in more than one location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>194 (27.9)</td>
<td>66 (25.9)</td>
<td>260 (27.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>494 (71.1)</td>
<td>188 (73.7)</td>
<td>682 (71.8)</td>
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</tr>
<tr>
<td>Missing</td>
<td>7 (1.0)</td>
<td>1 (0.4)</td>
<td>8 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Most common method used for prescribing medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-written prescription order</td>
<td>574 (82.6)</td>
<td>214 (83.9)</td>
<td>788 (82.9)</td>
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</tr>
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<td>Telephone prescription order</td>
<td>38 (5.5)</td>
<td>6 (2.4)</td>
<td>44 (4.6)</td>
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<td>Electronic prescription order</td>
<td>79 (11.4)</td>
<td>35 (13.7)</td>
<td>114 (12.0)</td>
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<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Use of electronic medical records at primary practice site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>144 (20.7)</td>
<td>55 (21.6)</td>
<td>199 (20.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>545 (78.4)</td>
<td>200 (78.4)</td>
<td>745 (78.4)</td>
<td>0.82</td>
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<tr>
<td>Missing</td>
<td>6 (0.9)</td>
<td>0 (0.0)</td>
<td>6 (0.6)</td>
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</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience (in years) in prescribing medicines</td>
<td>25.2 (10.1)</td>
</tr>
<tr>
<td>Patients seen/day</td>
<td>31.7 (30.2)</td>
</tr>
<tr>
<td>Hours per week seeing patients</td>
<td>38.1 (16.2)</td>
</tr>
</tbody>
</table>

SD = standard deviation.
*Percentages may not total 100 because of rounding.
Of the combined sample, 80.6% were male, 92.4% were physicians, 49.6% were cases, and 87.5% reported having national board certification. The respondents reported being a practicing licensed prescriber for 23.9 ± 10.8 years, saw 31.3 ± 30.1 patients per day, and spent 37.7 ± 15.7 hours per week seeing patients. With respect to the practice characteristics, approximately half of the combined sample reported office-based group practice as their primary practice site, another one-third primarily practiced in office-based solo practice, 71.8% practiced in only one location, 78.4% did not use electronic medical records at their primary practice site, 58.5% provided care for patients outside usual panel when on-call, and 82.9% used hand-written prescription order most commonly for prescribing medications. Interestingly, among the 199 prescribers who used electronic medical records at their primary practice site, 51.3% used hand-written prescription order most commonly for prescribing medications while 45.7% and 2.5% used electronic and telephone prescription order, respectively.

4.3 Prescribers’ General Opinions about DDIs

The majority of the respondents reported that the risk for a drug interaction somewhat (36.0%) or very much (55.7%) affected their selection of a drug product. Approximately three-fourths of the respondents (72.1%) reported they had seen a patient who had a drug interaction that caused temporary or permanent harm. A vast majority of the respondents (80.6%) believed that interactions were more frequently caused by drugs that were prescribed by two different prescribers, rather than the same prescriber. The respondents asked their patients about the use of prescription drugs more frequently
than over-the-counter products (OTC) and complimentary / alternative products (Table 4.2). Almost all the respondents (98.1%) usually or always asked patients about their use of prescription drugs compared to 75.4% and 52.6% for OTC products and complimentary / alternative products, respectively (Table 4.2).

Table 4.2 Prescribers perception of frequency for asking about their patients’ use of pharmaceutical products

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
</tr>
<tr>
<td>OTC products</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Complimentary/alternative</td>
<td>24 (2.5)</td>
</tr>
</tbody>
</table>

4.4 Prescribers’ Recognition of Drug-Drug Interaction

The distribution of responses for prescribers’ knowledge of the 14 DDI knowledge items is presented in Table 4.3. The cells in bold type are the correct answers. Missing data and the “not sure” responses were considered incorrect answers. The percentages of prescribers who answered the item correctly ranged from 18.2% for warfarin and cimetidine to 81.2% for drug pair amoxicillin and acetaminophen with codeine. Half of
the drug pair items were answered “not sure” by over one-third of the respondents. Among the four contraindicated drugs pairs (i.e., warfarin with cimetidine, methotrexate with trimethoprim-sulfamethoxazole, sildenafil with isosorbide mononitrate, and alprazolam with itraconazole), three (warfarin with cimetidine, methotrexate with trimethoprim-sulfamethoxazole, and alprazolam with itraconazole) were correctly categorized by less than one-fourth of the respondents. With respect to the two interacting pairs that require monitoring (i.e., cyclosporine with rifampin, and digoxin with clarithromycin), digoxin-clarithromycin was correctly categorized by half (49.5%) of the respondents, whereas cyclosporine-rifampin was recognized by only around one-fifth (19.2%). The mean percentage of items answered correctly was 42.7%.

The distribution of the number of items answered correctly is presented in Table 4.4. The total number of items answered correctly by the prescribers ranged from zero to thirteen items, with a mean of 6.0 ± 3.1 items. Two-thirds of the respondents answered half or fewer of the items correctly, and none could categorize all fourteen drug pairs correctly.
<table>
<thead>
<tr>
<th>Prescribers’ knowledge of DDIs</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Should not be used together (contra-indicated)</td>
</tr>
<tr>
<td>a. Coumadin® and Tagamet® (warfarin and cimetidine)</td>
<td>173 (18.2)</td>
</tr>
<tr>
<td>b. Viagra® and Wellbutrin® (sildenafil and bupropion)</td>
<td>53 (5.6)</td>
</tr>
<tr>
<td>c. Rheumatrex® and Bactrim DS® (methotrexate and trimethoprim-sulfamethoxazole)</td>
<td><strong>229 (24.1)</strong></td>
</tr>
<tr>
<td>d. Neoral ® and Rifadin ® (cyclosporine and rifampin)</td>
<td>202 (21.3)</td>
</tr>
<tr>
<td>e. Coumadin® and Calan® (warfarin and verapamil)</td>
<td>44 (4.6)</td>
</tr>
<tr>
<td>f. Valtrex® and Zocor® (valacyclovir and simvastatin)</td>
<td>61 (6.4)</td>
</tr>
<tr>
<td>g. Amoxil® and Tylenol #3® (amoxicillin and acetaminophen with codeine)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>h. Tenormin® and Zantac® (atenolol and ranitidine)</td>
<td>12 (1.3)</td>
</tr>
<tr>
<td>i. Lanoxin® and Biaxin® (digoxin and clarithromycin)</td>
<td>137 (14.4)</td>
</tr>
<tr>
<td>j. Micronase® and Fosamax® (glyburide and alendronate)</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>k. Viagra® and Imdur® (sildenafil and isosorbide mononitrate)</td>
<td><strong>767 (80.7)</strong></td>
</tr>
<tr>
<td>l. Ambien® and Ditropan® (zolpidem and oxybutinin)</td>
<td>59 (6.2)</td>
</tr>
<tr>
<td>m. Symmetrel® and Atrovent® (amantadine and ipratropium bromide)</td>
<td>52 (5.5)</td>
</tr>
<tr>
<td>n. Xanax® and Sporanox® (alprazolam and itraconazole)</td>
<td><strong>202 (21.3)</strong></td>
</tr>
</tbody>
</table>

Note: Cells in bold type represent correct answers.
*Percentages may not total 100 because of rounding.
Table 4.4 Number of DDI items answered correctly by respondents

<table>
<thead>
<tr>
<th>Number of items answered correctly</th>
<th>Frequency (%)</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>47 (4.9)</td>
<td>4.9</td>
</tr>
<tr>
<td>1</td>
<td>45 (4.7)</td>
<td>9.7</td>
</tr>
<tr>
<td>2</td>
<td>46 (4.8)</td>
<td>14.5</td>
</tr>
<tr>
<td>3</td>
<td>82 (8.6)</td>
<td>23.2</td>
</tr>
<tr>
<td>4</td>
<td>79 (8.3)</td>
<td>31.5</td>
</tr>
<tr>
<td>5</td>
<td>110 (11.6)</td>
<td>43.1</td>
</tr>
<tr>
<td>6</td>
<td>119 (12.5)</td>
<td>55.6</td>
</tr>
<tr>
<td>7</td>
<td>103 (10.8)</td>
<td>66.4</td>
</tr>
<tr>
<td>8</td>
<td>94 (9.9)</td>
<td>76.3</td>
</tr>
<tr>
<td>9</td>
<td>86 (9.1)</td>
<td>85.4</td>
</tr>
<tr>
<td>10</td>
<td>79 (8.3)</td>
<td>93.7</td>
</tr>
<tr>
<td>11</td>
<td>41 (4.3)</td>
<td>98.0</td>
</tr>
<tr>
<td>12</td>
<td>15 (1.6)</td>
<td>99.6</td>
</tr>
<tr>
<td>13</td>
<td>4 (0.4)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Prescribers’ responses to the DDI knowledge test were fitted into the 1-PL, 2-PL, and 3-PL models using the BILOG-MG 3 software. Analysis results revealed that the (-2 log likelihood) values of the 1-PL, 2-PL, and 3-PL models were 14,370, 13,946, and 14,128, respectively. The difference in (-2 log likelihood) value between 1-PL and 2PL models, and that between 2-PL and 3-PL models were 424 and 182, respectively. Both differences were statistically significant based on the critical chi-squared value with 14 degrees of freedom at the 0.05 level, which is 23.7. As such, the 2-PL model had a significantly lower (-2 log likelihood) value than the other two models and was considered to be the best fitting one. However, the greatest (-2 log likelihood) value of the 1-PL model did not necessarily indicate poor model-data-fit because log likelihood...
statistic is sensitive to sample size. As such, the WINSTEPS software was used to determine if the data fitted the 1-PL, or Rasch, model.

Rasch analysis showed that item reliability was 1.00 and person reliability was 0.72. Based on the predetermined criteria, only one item (i.e., warfarin and cimetidine) misfitted (outfit MNSQ = 2.21). After re-consideration and discussion, the research group decided to take both “contraindicated” and “use with monitoring” as correct answers for drug pairs warfarin with cimetidine and digoxin with clarithromycin. Prescribers’ responses were re-scored accordingly.

Item difficulty estimates and fit statistics after re-scoring are presented in Table 4.5. Person reliability slightly increased from 0.72 to 0.76, and both infit and outfit MNSQ of the two re-scored items decreased. Based on the predetermined criteria, none of the items misfitted, which indicated that these items functioned unidimensionally. A scree test in the principal component analysis revealed that the first eigenvalue was considerably greater than the other eigenvalues (1st eigenvalue = 3.8; 2nd eigenvalue = 1.4; 3rd eigenvalue = 1.1; 4th eigenvalue = 1.0; 5th eigenvalue = 0.9), which also indicated the unidimensionality of the data.

As presented in Table 4.5, item difficulty estimates ranged from -2.27 logits to 1.93 logits, with a mean of 0.00 and a standard deviation of 1.52. In WINSTEPS, a logit value of zero is arbitrarily set as the average of the item difficulty estimates. Item difficulty indicates the probability of correctly answering the item; the greater the value of item difficulty, the lower the probability of the item being answered correctly, thus the more difficult the item. As indicated by the item difficulty estimates, the most difficult
item in the DDI knowledge test was drug pair \( d \) (i.e., cyclosporine and rifampin), whereas the easiest items were drug pairs \( g \) (i.e., amoxicillin and acetaminophen with codeine) and \( a \) (i.e., warfarin and cimetidine). Because logit is an equal-interval unit, equal differences in item difficulty have the same meaning. For example, drug pair \( n \) was as much more difficult than drug pair \( c \) as drug pair \( b \) was more difficult than \( j \). The difference in item difficulty estimate between \( n \) and \( c \) was equal to that between \( b \) and \( j \) (0.21 logits).

Using the Rasch model, a score indicating prescribers’ DDI knowledge was calculated for each respondent. The overall mean knowledge score was \( 0.16 \pm 1.70 \) logits, with a range from -4.8 to 3.3.

<table>
<thead>
<tr>
<th>Drug pair</th>
<th>Item difficulty</th>
<th>Infit MNSQ</th>
<th>Outfit MNSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>d. cyclosporine and rifampin</td>
<td>1.93</td>
<td>1.11</td>
<td>1.29</td>
</tr>
<tr>
<td>n. alprazolam and itraconazole</td>
<td>1.76</td>
<td>1.00</td>
<td>1.33</td>
</tr>
<tr>
<td>c. methotrexate and trimethoprim-sulfamethoxazole</td>
<td>1.55</td>
<td>1.19</td>
<td>1.36</td>
</tr>
<tr>
<td>m. amantadine and ipratropium bromide</td>
<td>1.46</td>
<td>1.11</td>
<td>1.08</td>
</tr>
<tr>
<td>l. zolpidem and oxybutynin</td>
<td>0.81</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>e. warfarin and verapamil</td>
<td>0.81</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>f. valacyclovir and simvastatin</td>
<td>0.56</td>
<td>0.88</td>
<td>0.81</td>
</tr>
<tr>
<td>b. sildenafil and bupropion</td>
<td>-0.04</td>
<td>0.85</td>
<td>0.81</td>
</tr>
<tr>
<td>j. glyburide and alendronate</td>
<td>-0.25</td>
<td>0.79</td>
<td>0.71</td>
</tr>
<tr>
<td>i. digoxin and clarithromycin</td>
<td>-0.89</td>
<td>1.14</td>
<td>1.13</td>
</tr>
<tr>
<td>h. atenolol and ranitidine</td>
<td>-0.93</td>
<td>0.90</td>
<td>0.86</td>
</tr>
<tr>
<td>k. sildenafil and isosorbide mononitrate</td>
<td>-2.22</td>
<td>0.98</td>
<td>0.95</td>
</tr>
<tr>
<td>g. amoxicillin and acetaminophen with codeine</td>
<td>-2.27</td>
<td>0.99</td>
<td>0.76</td>
</tr>
<tr>
<td>a. warfarin and cimetidine</td>
<td>-2.27</td>
<td>1.15</td>
<td>1.74</td>
</tr>
</tbody>
</table>
The Rasch analysis person-item map is presented in Figure 4.1. The logit scale, which is the measurement unit common to both prescribers’ DDI knowledge and item difficulty, is displayed down the middle of the map. The logit scale is an interval scale so equal distances anywhere up and down the line have an equal value. This map provided a visual representation of the distribution and hierarchical order of prescribers’ DDI knowledge and item difficulty estimates. Prescribers’ DDI knowledge estimates are shown on the left of the scale and item difficulty estimates are presented on the right. As shown in the figure, again, the most difficult item was drug pair $d$, whereas the easiest items were drug pairs $a$, $g$, and $k$. In general, items and prescribers spreaded nicely along the scale, which indicated that the items targeted well on the prescribers’ DDI knowledge levels. Also, the distribution of prescribers seemed to be normal. Nevertheless, prescribers with little DDI knowledge were targeted by three items that were equally difficult, and these three items were still too difficult for some prescribers.
Figure 4.1 DDI knowledge test item and person map

Note: Each '#' represents 9 prescribers
M = mean; S = 1 standard deviation; T = 2 standard deviations
4.5 Demographic and Practice Factors Related to Prescribers’ DDI Knowledge

A multiple linear regression model was developed to examine the association between the knowledge scores and each potential predictor while controlling for the influences of other independent variables. Table 4.6 presents the results of the multiple regression analysis. The regression model explained 21.7% of the variance in scores. Analysis results revealed that a lower DDI knowledge score was associated with being a nurse practitioner practicing in an office-based solo practice. In addition, compared to general/family practitioners, a lower score was associated with having a specialty in psychiatry/neurology, surgery, obstetrics/gynecology, other specialty areas, pediatrics, or cardiology (in descending order of the unstandardized coefficient values). The results also indicated that a higher DDI knowledge score was associated with having previously seen a patient who had a DDI that caused harm. In addition, the prescribers who reported that the risk of DDI affected their selection of a drug product “very much” also had a higher score than those who reported that the risk affected their drug selection “a little” or “not at all”.

4.5.1 Results of Testing Hypothesis Ho₁

Ho₁: There is no difference in DDI knowledge between prescribers who had prescribed at least one interacting drug combination and prescribers who had no recent history of DDI prescribing.

To test hypothesis Ho₁, first, a two-sample t-test was used to compare the mean DDI knowledge scores that were derived from the Rasch analysis between cases and controls.
The cases had a slightly higher mean score than that of the controls (-0.05 and -0.26 logits, respectively), but the difference was not statistically significant ($p = 0.05$). As presented in Table 4.6, a multiple linear regression model revealed that cases and controls did not differ in DDI knowledge scores while the influences of other potential confounders were controlled for ($p = 0.51$).

Based on the analysis results, hypothesis Ho$_1$ was not rejected. It was concluded that there is no difference in DDI knowledge between prescribers who had prescribed at least one interacting drug combination and prescribers who had no recent history of DDI prescribing.

<table>
<thead>
<tr>
<th>Table 4.6 Regression coefficients for independent predictors of the DDI knowledge score</th>
<th>Coefficient</th>
<th>SE</th>
<th>$p$-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.01</td>
<td>0.33</td>
<td>0.98</td>
<td>-0.64</td>
</tr>
<tr>
<td>Female</td>
<td>-0.21</td>
<td>0.16</td>
<td>0.19</td>
<td>-0.51</td>
</tr>
<tr>
<td>Controls (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>0.07</td>
<td>0.11</td>
<td>0.51</td>
<td>-0.14</td>
</tr>
<tr>
<td>Patients seen/day</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.96</td>
<td>0.00</td>
</tr>
<tr>
<td>Hours per week seeing patients</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.98</td>
<td>-0.01</td>
</tr>
<tr>
<td>Years in prescribing medicines</td>
<td>-0.01</td>
<td>0.01</td>
<td>0.08</td>
<td>-0.02</td>
</tr>
<tr>
<td>Physician (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>0.37</td>
<td>0.37</td>
<td>0.32</td>
<td>-0.36</td>
</tr>
<tr>
<td>OP</td>
<td>0.22</td>
<td>0.34</td>
<td>0.50</td>
<td>-0.43</td>
</tr>
<tr>
<td>Office-based practice-group (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office-based practice-solo</td>
<td>-0.02</td>
<td>0.12</td>
<td>0.85</td>
<td>-0.26</td>
</tr>
<tr>
<td>Hospital-based clinic</td>
<td>0.35</td>
<td>0.23</td>
<td>0.13</td>
<td>-0.11</td>
</tr>
<tr>
<td>Hospital acute care</td>
<td>&lt;0.01</td>
<td>0.36</td>
<td>&gt; 0.99</td>
<td>-0.70</td>
</tr>
<tr>
<td>Others</td>
<td>0.32</td>
<td>0.25</td>
<td>0.21</td>
<td>-0.18</td>
</tr>
</tbody>
</table>
Table 4.6 Regression coefficients for independent predictors of the DDI knowledge score (cont.)

<table>
<thead>
<tr>
<th>Category</th>
<th>Coefficient</th>
<th>SE</th>
<th>p- value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General / Family practice (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics and Gynecology</td>
<td>-1.44</td>
<td>0.30</td>
<td>&lt; 0.001</td>
<td>-2.02 -0.85</td>
</tr>
<tr>
<td>Internal Medicine (other than cardiology)</td>
<td>-0.20</td>
<td>0.13</td>
<td>0.12</td>
<td>-0.46 0.05</td>
</tr>
<tr>
<td>Cardiology</td>
<td>-0.93</td>
<td>0.22</td>
<td>&lt; 0.001</td>
<td>-1.37 -0.49</td>
</tr>
<tr>
<td>Surgery</td>
<td>-1.81</td>
<td>0.29</td>
<td>&lt; 0.001</td>
<td>-2.37 -1.25</td>
</tr>
<tr>
<td>Psychiatry and Neurology</td>
<td>-2.05</td>
<td>0.21</td>
<td>&lt; 0.001</td>
<td>-2.46 -1.64</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>-1.19</td>
<td>0.31</td>
<td>&lt; 0.001</td>
<td>-1.80 -0.57</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>-0.05</td>
<td>0.39</td>
<td>0.91</td>
<td>-0.80 0.71</td>
</tr>
<tr>
<td>Others</td>
<td>-1.28</td>
<td>0.21</td>
<td>&lt; 0.001</td>
<td>-1.69 -0.87</td>
</tr>
<tr>
<td>Hand-written prescription order (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic prescription order</td>
<td>0.28</td>
<td>0.19</td>
<td>0.14</td>
<td>-0.09 0.65</td>
</tr>
<tr>
<td>Telephone prescription order</td>
<td>-0.29</td>
<td>0.25</td>
<td>0.24</td>
<td>-0.78 0.19</td>
</tr>
<tr>
<td>Did not use electronic medical records (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used electronic medical records</td>
<td>-0.20</td>
<td>0.15</td>
<td>0.19</td>
<td>-0.50 0.10</td>
</tr>
<tr>
<td>The risk for a DDI a little or not at all affected drug selection (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat</td>
<td>0.29</td>
<td>0.20</td>
<td>0.16</td>
<td>-0.11 0.69</td>
</tr>
<tr>
<td>Very much</td>
<td>0.48</td>
<td>0.20</td>
<td>0.02</td>
<td>0.09 0.87</td>
</tr>
<tr>
<td>Had not seen a DDI caused harm (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had seen a DDI caused harm</td>
<td>0.24</td>
<td>0.12</td>
<td>0.05</td>
<td>0.01 0.48</td>
</tr>
<tr>
<td>Physician* Office-based practice-group (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP*Office-based practice-solo</td>
<td>-1.69</td>
<td>0.68</td>
<td>0.01</td>
<td>-3.03 -0.35</td>
</tr>
<tr>
<td>NP*Hospital-based clinic</td>
<td>-0.15</td>
<td>1.63</td>
<td>0.93</td>
<td>-3.34 3.04</td>
</tr>
<tr>
<td>NP*Other practice sites</td>
<td>-0.53</td>
<td>0.88</td>
<td>0.54</td>
<td>-2.26 1.19</td>
</tr>
<tr>
<td>Other professions*Office-based practice-solo</td>
<td>-0.53</td>
<td>0.66</td>
<td>0.42</td>
<td>-1.82 0.76</td>
</tr>
<tr>
<td>OP*Hospital-based clinic</td>
<td>2.07</td>
<td>1.60</td>
<td>0.20</td>
<td>-1.07 5.22</td>
</tr>
<tr>
<td>OP*Hospital acute care</td>
<td>-0.23</td>
<td>1.62</td>
<td>0.89</td>
<td>-3.41 2.94</td>
</tr>
<tr>
<td>OP*Other practice sites</td>
<td>-1.64</td>
<td>1.63</td>
<td>0.32</td>
<td>-4.84 1.56</td>
</tr>
</tbody>
</table>

Ref = reference group; NP = nurse practitioner; OP = other professions; SE = standard error; CI = confidence interval.
Note: Overall $F_{(33,879)} = 7.38$ ($p < 0.001$); R-square = 0.22; adjusted R-square = 0.19.
4.5.2 Results of Testing Hypothesis Ho2

*Ho2*: The prescribers who had prescribed at least one interacting drug combination were equally likely to answer the DDI of interest question correctly as the prescribers who had no recent history of prescribing such an interacting drug combination.

In addition to the fourteen common drug pairs, the DDI knowledge test contained an item tailored to each individual prescriber (i.e., drug pair $o$). This item was the interacting drug pair by which the cases and controls were matched. In the case where this specific drug pair was already included in the test in items $a$ through $n$, drug pair $o$ would be replaced with drugs azathioprine and allopurinol, which is a drug pair that may be used together with monitoring. As such, the correct answer to drug pair $o$ depended on which drug pair the respondent was asked to categorize. Unfortunately, due to a printing error, drug pair $o$ printed on the Arizona survey questionnaire was not the pair the respondents were supposed to answer. As such, the following analysis included only the national respondents.

Among the 695 national respondents, 278, or 40%, of the respondents answered drug pair $o$ correctly. To test hypothesis Ho2, a logistic regression model was developed to examine whether the likelihood of correctly answering drug pair $o$ differed between cases and controls while controlling for potential confounders. All the independent variables in the previous multiple regression model were included in this logistic regression model. As presented in Table 4.7, analysis results indicated that cases and controls were equally likely to answer the DDI of interest question correctly ($p = 0.49$).

Based on the analysis result, hypothesis Ho2 was not rejected. It was concluded that
the prescribers who had prescribed at least one interacting drug combination were equally likely to answer the DDI of interest question correctly as the prescribers who had no recent history of prescribing such an interacting drug combination..

Table 4.7 Logistic regression coefficients for independent predictors of correctly answering drug pair \( o \)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>( p )- value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.61</td>
<td>0.55</td>
<td>0.27</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.06</td>
<td>0.26</td>
<td>0.81</td>
<td>1.07</td>
<td>0.64 1.79</td>
</tr>
<tr>
<td>Prescription volume</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.88</td>
<td>1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Patients seen/day</td>
<td>-0.01</td>
<td>&lt;0.01</td>
<td>0.03</td>
<td>0.99</td>
<td>0.99 1.00</td>
</tr>
<tr>
<td>Hours per week seeing patients</td>
<td>0.01</td>
<td>0.01</td>
<td>0.13</td>
<td>1.01</td>
<td>1.00 1.02</td>
</tr>
<tr>
<td>Years in prescribing medicines</td>
<td>-0.01</td>
<td>0.01</td>
<td>0.26</td>
<td>0.99</td>
<td>0.97 1.01</td>
</tr>
<tr>
<td>Physician (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>-0.11</td>
<td>0.97</td>
<td>0.91</td>
<td>0.90</td>
<td>0.13 6.03</td>
</tr>
<tr>
<td>OP</td>
<td>-1.17</td>
<td>1.13</td>
<td>0.30</td>
<td>0.31</td>
<td>0.03 2.82</td>
</tr>
<tr>
<td>General / Family practice (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics and Gynecology</td>
<td>-0.13</td>
<td>0.45</td>
<td>0.78</td>
<td>0.88</td>
<td>0.36 2.13</td>
</tr>
<tr>
<td>Internal Medicine (other than cardiology)</td>
<td>0.35</td>
<td>0.22</td>
<td>0.10</td>
<td>1.42</td>
<td>0.93 2.16</td>
</tr>
<tr>
<td>Cardiology</td>
<td>0.40</td>
<td>0.38</td>
<td>0.30</td>
<td>1.49</td>
<td>0.70 3.17</td>
</tr>
<tr>
<td>Surgery</td>
<td>-0.87</td>
<td>0.50</td>
<td>0.08</td>
<td>0.42</td>
<td>0.16 1.13</td>
</tr>
<tr>
<td>Psychiatry and Neurology</td>
<td>0.47</td>
<td>0.33</td>
<td>0.15</td>
<td>1.59</td>
<td>0.84 3.01</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>-0.72</td>
<td>0.54</td>
<td>0.19</td>
<td>0.49</td>
<td>0.17 1.41</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>0.98</td>
<td>0.70</td>
<td>0.16</td>
<td>2.67</td>
<td>0.69 10.43</td>
</tr>
<tr>
<td>Others</td>
<td>-0.31</td>
<td>0.34</td>
<td>0.37</td>
<td>0.74</td>
<td>0.38 1.44</td>
</tr>
<tr>
<td>Office-based practice-group (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office-based practice-solo</td>
<td>0.27</td>
<td>0.19</td>
<td>0.15</td>
<td>1.31</td>
<td>0.91 1.90</td>
</tr>
<tr>
<td>Hospital-based clinic</td>
<td>0.59</td>
<td>0.36</td>
<td>0.10</td>
<td>1.81</td>
<td>0.90 3.63</td>
</tr>
<tr>
<td>Hospital acute care</td>
<td>-0.99</td>
<td>0.63</td>
<td>0.12</td>
<td>0.37</td>
<td>0.11 1.28</td>
</tr>
<tr>
<td>Others</td>
<td>-1.45</td>
<td>0.61</td>
<td>0.02</td>
<td>0.24</td>
<td>0.07 0.78</td>
</tr>
</tbody>
</table>
Table 4.7 Logistic regression coefficients for independent predictors of correctly answering drug pair (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>SE</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>-0.13</td>
<td>0.19</td>
<td>0.49</td>
<td>0.88</td>
<td>0.61</td>
</tr>
<tr>
<td>Hand-written prescription order (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic prescription order</td>
<td>&lt;0.01</td>
<td>0.30</td>
<td>&gt;0.99</td>
<td>1.00</td>
<td>0.55</td>
</tr>
<tr>
<td>Telephone prescription order</td>
<td>-0.75</td>
<td>0.41</td>
<td>0.07</td>
<td>0.47</td>
<td>0.21</td>
</tr>
<tr>
<td>Did not use electronic medical records (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used electronic medical records</td>
<td>-0.09</td>
<td>0.25</td>
<td>0.73</td>
<td>0.92</td>
<td>0.57</td>
</tr>
<tr>
<td>The risk for a DDI a little or not at all affected drug selection (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat</td>
<td>-0.07</td>
<td>0.32</td>
<td>0.84</td>
<td>0.94</td>
<td>0.50</td>
</tr>
<tr>
<td>Very much</td>
<td>0.03</td>
<td>0.31</td>
<td>0.93</td>
<td>1.03</td>
<td>0.57</td>
</tr>
<tr>
<td>Had not seen a DDI caused harm (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had seen a DDI caused harm</td>
<td>0.44</td>
<td>0.20</td>
<td>0.03</td>
<td>1.55</td>
<td>1.05</td>
</tr>
<tr>
<td>Physician* Office-based practice-group (Ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP*Office-based practice-solo</td>
<td>0.35</td>
<td>1.71</td>
<td>0.84</td>
<td>1.42</td>
<td>0.05</td>
</tr>
<tr>
<td>NP*Hospital-based clinic</td>
<td>22.32</td>
<td>40192.97</td>
<td>&gt;0.99</td>
<td>&gt;1000</td>
<td>0.00</td>
</tr>
<tr>
<td>OP*Office-based practice-solo</td>
<td>-19.17</td>
<td>16267.84</td>
<td>&gt;0.99</td>
<td>&lt;0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>OP*Hospital-based clinic</td>
<td>23.35</td>
<td>40192.97</td>
<td>&gt;0.99</td>
<td>&gt;1000</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Ref = reference group; NP = nurse practitioner; OP = other professions; SE = standard error; OR = odds ratio; CI = confidence interval; NA = not available.
Note: Chi-square (30) = 65.08 (p < 0.001); Cox & Snell R-square = 0.093; Nagelkerke R-square = 0.13; -2 log likelihood = 830.83.

4.6 Prescribers’ Sources of DDI Information

Table 4.8 provides the frequency of the prescribers’ responses to two questions relating to the prescribers’ DDI information sources. When the prescribers wanted to learn more
about an interaction, one-fourth used PDAs and another one-fourth used printed materials. The next most commonly used references were package insert and pharmacists, each reported by 14.2% of the respondents. Less than 5% of the prescribers relied on the Internet when they wanted to learn about an interaction. According to 68.4% of the respondents, when a patient was about to be exposed to a potential DDI, it was pharmacists who usually informed the respondents. The next most frequently reported DDI information source was PDAs (15.8% of the respondents), followed by computerized alert systems (10.8%) and other sources (5.1%).

Table 4.8 Prescribers’ sources of DDI information

Q: When you want to learn more about an interaction, what reference/person do you use?

<table>
<thead>
<tr>
<th>Source</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package insert</td>
<td>45 (14.2)</td>
</tr>
<tr>
<td>Computerized alert system</td>
<td>26 (8.2)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>45 (14.2)</td>
</tr>
<tr>
<td>Printed materials</td>
<td>76 (24.1)</td>
</tr>
<tr>
<td>Personal digital asst. (PDA)</td>
<td>82 (25.9)</td>
</tr>
<tr>
<td>Internet</td>
<td>13 (4.1)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (9.2)</td>
</tr>
</tbody>
</table>

Q: When one of your patients is about to be exposed to a potential drug interaction, who usually informs you that the interaction may be present?

<table>
<thead>
<tr>
<th>Source</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacist</td>
<td>216 (68.4)</td>
</tr>
<tr>
<td>Computerized alert system</td>
<td>34 (10.8)</td>
</tr>
<tr>
<td>Personal digital assistant (PDA)</td>
<td>50 (15.8)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (5.1)</td>
</tr>
</tbody>
</table>
4.6.1 Results of Testing Hypothesis Ho3

Ho3: There is no difference in DDI knowledge among prescribers who usually consult written, electronic, or personal information source for DDI information.

To test hypothesis Ho3, ANOVA was used to compare the DDI knowledge scores, which were derived from the Rasch analysis, among prescribers who consult different sources to learn more about DDIs. For this comparison, prescribers who used PDAs and the Internet were put into one group (i.e., electronic references), whereas those who used package inset and printed materials were put into another group (i.e., written references). In addition, the prescribers who selected “other” references and specified which one was used were put into either the “electronic references” or the “written references” group depending on the type of reference used. Five prescribers were excluded from the analysis either because they did not specify which reference they used or the reference reported could not be categorized. After re-grouping, the knowledge scores of four groups of prescribers were compared in the ANOVA analysis: pharmacists, written references, electronic references, and computerized alert systems. The analysis result is presented in Table 4.9. The mean DDI knowledge scores of the four groups of prescribers were -0.55, 0.00, 0.29, and 0.55 logits, respectively. The ANOVA analysis revealed a significant difference among the four source groups ($p = 0.004$). The Scheffe test (Table 4.10) indicated that prescribers who consulted electronic references or computerized alert systems for DDI information had a higher DDI knowledge score than those who consulted pharmacists.

Based on the analysis results, hypothesis Ho3 was rejected. It was found that there
was a difference in DDI knowledge among prescribers who usually consult written, electronic, or personal information source for DDI information. Specifically, prescribers who consulted electronic references or computerized alert systems for DDI information had a higher DDI knowledge score than those who consulted pharmacists.

### Table 4.9 Comparison of mean DDI knowledge scores among prescribers who consult different sources to learn more about DDIs

<table>
<thead>
<tr>
<th></th>
<th>Sum of squares</th>
<th>Degree of freedom</th>
<th>Mean square</th>
<th>F-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between</td>
<td>29.03</td>
<td>3</td>
<td>9.68</td>
<td>4.47</td>
<td>0.004</td>
</tr>
<tr>
<td>Within</td>
<td>666.27</td>
<td>308</td>
<td>2.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>695.30</td>
<td>311</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4.10 Scheffe test for comparing mean DDI knowledge scores among prescribers who consult different sources to learn more about DDIs

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Mean difference</th>
<th>Standard error</th>
<th>p-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>Written DDI alerts</td>
<td>-0.55</td>
<td>0.31</td>
<td>0.38</td>
<td>-1.44</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>0.55</td>
<td>0.25</td>
<td>0.19</td>
<td>-0.16</td>
</tr>
<tr>
<td>Electronic</td>
<td>-0.29</td>
<td>0.19</td>
<td>0.53</td>
<td>-0.83</td>
</tr>
<tr>
<td>Written DDI alerts</td>
<td>0.55</td>
<td>0.31</td>
<td>0.38</td>
<td>-0.33</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>1.10</td>
<td>0.36</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Electronic</td>
<td>0.27</td>
<td>0.32</td>
<td>0.88</td>
<td>-0.64</td>
</tr>
<tr>
<td>Written Pharmacist</td>
<td>-0.55</td>
<td>0.25</td>
<td>0.19</td>
<td>-1.25</td>
</tr>
<tr>
<td>DDI alerts</td>
<td>-1.10</td>
<td>0.36</td>
<td>0.03</td>
<td>-2.12</td>
</tr>
<tr>
<td>Electronic</td>
<td>-0.83</td>
<td>0.26</td>
<td>0.02</td>
<td>-1.57</td>
</tr>
<tr>
<td>Written Electronic</td>
<td>0.29</td>
<td>0.19</td>
<td>0.53</td>
<td>-0.25</td>
</tr>
<tr>
<td>DDI alerts</td>
<td>0.27</td>
<td>0.32</td>
<td>0.88</td>
<td>-1.18</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>0.83</td>
<td>0.26</td>
<td>0.02</td>
<td>0.10</td>
</tr>
</tbody>
</table>
### 4.6.2 Prescribers’ Evaluation of Their Usual Sources of DDI Information

Table 4.11 presents prescribers’ mean ratings on five statements about their usual sources of DDI information. As indicated by the mean ratings, prescribers reported that their usual source of DDI information contained sufficient information to manage the interaction and the information was useful in future prescribing decisions. About half of the respondents found that the information usually or always changed their initial prescribing decisions. Also, half of the respondents found that the information was usually or always relevant to the patient. However, the information was not always new to the prescribers; only 13.9% found the information usually or always new.

As presented in Table 4.11, prescribers who used computerized DDI alerts as their usual source of DDI information consistently gave a lower rating score to the five statements than those who used the other three sources. Compared to the prescribers who used pharmacists, DDI alerts, or PDAs as their information source, a higher percentage of the prescribers who used “other” sources reported that the information often changed initial prescribing decisions and that the information was often relevant to the patient, sufficient to manage the interaction, and useful in future prescribing. However, only a few prescribers who reported using “other” sources specified what the source was; examples included the prescriber himself / herself and reference books.

ANOVA indicated a significant difference in mean rating scores among the four source groups for two statements: whether the information was relevant to the patient ($F_{3,311} = 6.88, p < 0.001$) and whether the information was useful in future prescribing ($F_{3,312} = 3.40, p = 0.02$). The Scheffe test indicated that DDI information provided by “other”
sources was more often useful to the prescriber in future prescribing than that provided by computerized DDI alerts \( (p = 0.03) \). In addition, DDI information provided by “other” sources was more often relevant to the patient than that provided by pharmacists, DDI alerts, or PDAs \( (p < 0.05) \). No other significant differences among the groups were detected.

Table 4.11 Prescribers’ views about their usual source of DDI information

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Pharmacist</th>
<th>DDI alert system</th>
<th>PDA</th>
<th>Other</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often does the drug</td>
<td>3.5</td>
<td>3.6</td>
<td>3.2</td>
<td>3.6</td>
<td>3.5</td>
<td>0.09</td>
</tr>
<tr>
<td>interaction information</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(1.0)</td>
<td></td>
</tr>
<tr>
<td>change your initial</td>
<td>[49.1]</td>
<td>[51.9]</td>
<td>[32.3]</td>
<td>[46.0]</td>
<td>[56.3]</td>
<td></td>
</tr>
<tr>
<td>prescribing decisions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How often is the drug</td>
<td>3.0</td>
<td>3.1</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td>0.19</td>
</tr>
<tr>
<td>interaction information</td>
<td>(0.5)</td>
<td>(0.5)</td>
<td>(0.4)</td>
<td>(0.6)</td>
<td>(0.6)</td>
<td></td>
</tr>
<tr>
<td>new to you?</td>
<td>[13.9]</td>
<td>[15.7]</td>
<td>[5.9]</td>
<td>[12.0]</td>
<td>[12.5]</td>
<td></td>
</tr>
<tr>
<td>How often is the drug</td>
<td>3.6</td>
<td>3.5</td>
<td>3.2</td>
<td>3.7</td>
<td>4.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>interaction information</td>
<td>(0.9)</td>
<td>(0.9)</td>
<td>(0.7)</td>
<td>(0.7)</td>
<td>(1.0)</td>
<td></td>
</tr>
<tr>
<td>relevant to the patient?</td>
<td>[49.3]</td>
<td>[49.8]</td>
<td>[26.5]</td>
<td>[54.0]</td>
<td>[81.3]</td>
<td></td>
</tr>
<tr>
<td>Is the drug interaction</td>
<td>3.8</td>
<td>3.8</td>
<td>3.7</td>
<td>3.8</td>
<td>4.1</td>
<td>0.39</td>
</tr>
<tr>
<td>information sufficient for</td>
<td>(0.6)</td>
<td>(0.7)</td>
<td>(0.6)</td>
<td>(0.4)</td>
<td>(0.7)</td>
<td></td>
</tr>
<tr>
<td>you to manage the interaction?</td>
<td>[80.1]</td>
<td>[79.1]</td>
<td>[76.4]</td>
<td>[82.0]</td>
<td>[93.8]</td>
<td></td>
</tr>
<tr>
<td>How often is the drug</td>
<td>4.0</td>
<td>4.0</td>
<td>3.7</td>
<td>4.0</td>
<td>4.4</td>
<td>0.02</td>
</tr>
<tr>
<td>interaction information</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.7)</td>
<td></td>
</tr>
<tr>
<td>useful to you in future</td>
<td>[78.2]</td>
<td>[79.2]</td>
<td>[58.9]</td>
<td>[84.0]</td>
<td>[87.5]</td>
<td></td>
</tr>
<tr>
<td>prescribing?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; DDI = drug-drug interaction; PDA = personal digital assistant.
*1 = Never 2 = Seldom 3 = Sometimes 4 = Usually 5 = Always.
†Includes those responded usually and always.
Data were further analyzed with the RSM using the WINSTEPS software. Among the five items assessing the usefulness of DDI information sources, the response category “never” was used only once by one respondent. In order to make the response categories function better in the analysis, response categories “never” and “seldom” were collapsed to make a new category “never or seldom”, and data were re-coded to reflect the change. After recoding, person reliability was 0.61, and item reliability was 0.99. Item difficulty estimates and fit statistics are presented in Table 4.12. Item difficulty refers to the probability of endorsement; the greater the value of item difficulty, the lower the probability of the item being endorsed. Among the five statements, the statement regarding the future usefulness of the information was most easily to endorse (item difficulty = -1.2 logits), whereas the statement regarding how often the information was new to the prescriber was most difficult to endorse (item difficulty = 1.68). Infit MNSQ ranged from 0.81 to 1.12; similarly, outfit MNSQ ranged from 0.81 to 1.11. Based on the predetermined criteria, none of the five items misfitted, which indicated that these five items functioned unidimensionally. A scree test in the principal component analysis identified one major factor of the data (1st eigenvalue = 2.0; 2nd eigenvalue = 1.1; 3rd eigenvalue = 0.8), which also indicated the unidimensionality of the data. This factor explained 40.8% of total variance.
Table 4.12 Statistics of the items in the DDI information source usefulness assessment

<table>
<thead>
<tr>
<th>Item</th>
<th>Infit</th>
<th>MNSQ</th>
<th>Outfit MNSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often is the drug interaction information new to you?</td>
<td>1.68</td>
<td>0.92</td>
<td>0.96</td>
</tr>
<tr>
<td>How often does the drug interaction information change your initial prescribing decisions?</td>
<td>0.17</td>
<td>1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>How often is the drug interaction information relevant to the patient?</td>
<td>0.08</td>
<td>1.12</td>
<td>1.11</td>
</tr>
<tr>
<td>Is the drug interaction information sufficient for you to manage the interaction?</td>
<td>-0.72</td>
<td>1.07</td>
<td>1.08</td>
</tr>
<tr>
<td>How often is the drug interaction information useful to you in future prescribing?</td>
<td>-1.20</td>
<td>0.81</td>
<td>0.81</td>
</tr>
</tbody>
</table>

As shown in Table 4.13, the average measures of all five items increased monotonically. Average measures are the average of the perception of usefulness scores for all prescribers who chose that particular response category. The observed monotonicity indicated that on average, prescribers who considered the information source always or usually useful endorsed the higher response categories, whereas those who considered the source seldom or sometimes useful endorsed lower response categories. In other words, the response categories functioned in the way we planned.
<table>
<thead>
<tr>
<th>Table 4.13 Average measures of the response categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response category</strong></td>
</tr>
<tr>
<td>How often is the drug interaction information new to you?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>How often does the drug interaction information change your initial prescribing decisions?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>How often is the drug interaction information relevant to the patient?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Is the drug interaction information sufficient for you to manage the interaction?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>How often is the drug interaction information useful to you in future prescribing?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Using the rating scale model, a score indicating prescribers’ attitudes toward the usefulness of the DDI information source was calculated for each respondent. The overall mean usefulness score was $0.25 \pm 1.45$ logits, with a range from -6.0 to 3.4. The mean usefulness scores of the DDI information provided by pharmacists, PDAs, computerized alert systems, and other sources were $0.28 \pm 1.53$, $0.32 \pm 1.04$, $-0.43 \pm 1.47$, and $1.04 \pm 0.80$ logits, respectively.
4.6.3 Results of Testing Hypothesis Ho4

Ho4: There is no difference among prescribers’ perceptions of the usefulness of pharmacists, computerized alert systems, personal digital assistants (PDAs), or other DDI information sources.

To test hypothesis Ho4, ANOVA was used to compare these IRT-derived usefulness scores among the four sources (Table 4.14). The analysis revealed a significant difference ($p = 0.006$). As presented in Table 4.15, the Scheffe test indicated that prescribers considered DDI information provided by “other” sources to be more useful than that provided by computerized alert systems ($p = 0.01$).

Based on the analysis results, hypothesis Ho4 was rejected. It was concluded that there is a difference among prescribers’ perceptions of the usefulness of pharmacists, computerized alert systems, personal digital assistants (PDAs), or other DDI information sources. Specifically, prescribers considered DDI information provided by “other” sources to be more useful than that provided by computerized alert systems.

<p>| Table 4.14 Comparison of mean usefulness scores among DDI information sources |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Sum of squares</th>
<th>Degree of freedom</th>
<th>Mean square</th>
<th>F-statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between</td>
<td>26.25</td>
<td>3</td>
<td>8.75</td>
<td>4.29</td>
</tr>
<tr>
<td>Within</td>
<td>636.52</td>
<td>312</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>662.77</td>
<td>315</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.15 Scheffe test for comparing mean usefulness scores among DDI information sources

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Mean difference</th>
<th>Standard error</th>
<th>p-value 95%</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDI alerts</td>
<td>0.71</td>
<td>0.26</td>
<td>0.07</td>
<td>-0.03, 1.45</td>
</tr>
<tr>
<td>PDA</td>
<td>-0.05</td>
<td>0.22</td>
<td>0.99</td>
<td>-0.68, 0.58</td>
</tr>
<tr>
<td>Other</td>
<td>-0.76</td>
<td>0.37</td>
<td>0.24</td>
<td>-1.80, 0.28</td>
</tr>
<tr>
<td>DDI alerts</td>
<td>-0.71</td>
<td>0.26</td>
<td>0.07</td>
<td>-1.45, 0.03</td>
</tr>
<tr>
<td>Pharmacist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDI alerts</td>
<td>-0.76</td>
<td>0.32</td>
<td>0.13</td>
<td>-1.65, 0.13</td>
</tr>
<tr>
<td>PDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>-1.47</td>
<td>0.43</td>
<td>0.01</td>
<td>-2.69, -0.26</td>
</tr>
<tr>
<td>PDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacist</td>
<td>0.05</td>
<td>0.22</td>
<td>0.99</td>
<td>-0.58, 0.68</td>
</tr>
<tr>
<td>DDI alerts</td>
<td>0.76</td>
<td>0.32</td>
<td>0.13</td>
<td>-0.14, 1.65</td>
</tr>
<tr>
<td>Other</td>
<td>-0.72</td>
<td>0.41</td>
<td>0.39</td>
<td>-1.87, 0.44</td>
</tr>
<tr>
<td>DDI alerts</td>
<td>1.47</td>
<td>0.43</td>
<td>0.01</td>
<td>0.26, 2.69</td>
</tr>
<tr>
<td>PDA</td>
<td>0.72</td>
<td>0.41</td>
<td>0.39</td>
<td>-0.44, 1.87</td>
</tr>
</tbody>
</table>

PDA = Personal digital assistant

4.7 Prescribers’ Opinions about Computerized DDI Alerts

Among the 61 respondents who completed and returned the long version of the national survey questionnaire, only 7 (11.5%) respondents used a CPOE system that provided DDI alerts for medication orders. In the Arizona survey, a similar percentage, 10.2% (26 respondents), reported using CPOE that provided DDI alerts in the respondents’ primary practice setting. Table 4.16 presents these 33 prescribers’ mean rating for each of a series of statements about computerized DDI alerts, among which, eight statements were included only in the Arizona survey. As the results indicated, 15.2% of the prescribers admitted that they usually or always overrode DDI alerts without properly checking them, whereas 33.3% reported that they seldom or never did.
More than 80% of the prescribers agreed that DDI alerts were useful tools in prescribing, were good at alerting the prescribers to significant interactions, and enabled the prescribers to prescribe more safely. Prescribers also agreed that there should be a greater distinction between important and less important interactions and that it should be more difficult to override alerts for potentially lethal interactions. However, only half of the prescribers (46.2%) were satisfied with the DDI alert system, and only one-fifth agreed that the information provided by the system was just about all he/she needed.
Table 4.16 Prescribers’ opinions about computerized DDI alerts

<table>
<thead>
<tr>
<th></th>
<th>mean* (SD)</th>
<th>% often†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anecdotal reports suggest that physicians believe that they</td>
<td>2.7 (0.8)</td>
<td>15.2</td>
</tr>
<tr>
<td>sometimes override interaction alerts without properly checking them. How often</td>
<td></td>
<td></td>
</tr>
<tr>
<td>does this happen to you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>There should be a greater distinction between important and less important</td>
<td>4.6 (0.8)</td>
<td>94.0</td>
</tr>
<tr>
<td>interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It should be more difficult to override alerts for potentially lethal</td>
<td>4.3 (1.0)</td>
<td>87.9</td>
</tr>
<tr>
<td>interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interaction alerts are a useful tool in prescribing.</td>
<td>4.1 (0.7)</td>
<td>87.8</td>
</tr>
<tr>
<td>Drug interaction alert systems are good at alerting me to</td>
<td>4.0 (0.7)</td>
<td>84.9</td>
</tr>
<tr>
<td>significant interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The information on the drug interaction alert system is not always reliable.</td>
<td>3.6 (0.9)</td>
<td>63.6</td>
</tr>
<tr>
<td>DDI alert system enables me to prescribe more safely.†‡</td>
<td>3.9 (0.5)</td>
<td>80.8</td>
</tr>
<tr>
<td>DDI alerts are sometimes not applicable / relevant to the patient.†‡</td>
<td>3.9 (0.8)</td>
<td>76.9</td>
</tr>
<tr>
<td>DDI alerts frequently provide me with information that I already know.†‡</td>
<td>3.7 (0.7)</td>
<td>65.4</td>
</tr>
<tr>
<td>I feel confident in the computer’s ability to provide me with meaningful DDI alerts.</td>
<td>3.5 (0.7)</td>
<td>57.6</td>
</tr>
<tr>
<td>Overall, I am satisfied with the DDI alert system.‡¶</td>
<td>3.3 (0.7)</td>
<td>46.2</td>
</tr>
<tr>
<td>I am satisfied with the format in which DDI alerts are provided.‡¶</td>
<td>3.1 (0.9)</td>
<td>42.3</td>
</tr>
<tr>
<td>DDI alerts are annoying.‡¶</td>
<td>2.9 (0.9)</td>
<td>30.8</td>
</tr>
<tr>
<td>The information provided by the DDI alert system is just about all I need.‡¶</td>
<td>2.8 (0.8)</td>
<td>20.0</td>
</tr>
</tbody>
</table>

SD = standard deviation.

*1 = Never, 2 = Seldom, 3 = Sometimes, 4 = Usually, 5 = Always.
†Includes those responded usually and always.
‡1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree.
§Includes those responded agree or strongly agree.
¶The questions were included in the Arizona survey only.
4.8 Summary of Hypothesis Test Results

Table 4.17 summarizes the results of all hypothesis tests. The first two hypotheses were not rejected. It was concluded that prescribers who had prescribed at least one interacting drug combination and prescribers who had no recent history of DDI prescribing did not differ in their DDI knowledge scores and the two groups of prescribers were equally likely to answer the DDI of interest question correctly.

Hypotheses Ho3 and Ho4 were rejected. It was found that prescribers who consulted electronic references or computerized alert systems for DDI information had a higher DDI knowledge score than those who consulted pharmacists. Also, prescribers considered DDI information provided by “other” sources to be more useful than that provided by computerized alert systems.

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Description</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho1</td>
<td>There is no difference in DDI knowledge between prescribers who had prescribed at least one interacting drug combination and prescribers who had no recent history of DDI prescribing.</td>
<td>Fail to reject</td>
</tr>
<tr>
<td>Ho2</td>
<td>The prescribers who had prescribed at least one interacting drug combination were equally likely to answer the DDI of interest question correctly as the prescribers who had no recent history of prescribing such an interacting drug combination.</td>
<td>Fail to reject</td>
</tr>
<tr>
<td>Ho3</td>
<td>There is no difference in DDI knowledge among prescribers who usually consult written, electronic, or personal information source for DDI information.</td>
<td>Rejected</td>
</tr>
<tr>
<td>Ho4</td>
<td>There is no difference among prescribers’ perceptions of the usefulness of pharmacists, computerized alert systems, personal digital assistants (PDAs), or other DDI information sources.</td>
<td>Rejected</td>
</tr>
</tbody>
</table>
CHAPTER 5
DISCUSSION

This chapter provides a discussion of the key findings of this research as well as the implications for health professionals and recommendations for future research based on the study results. The limitations of the study are then discussed, followed by conclusions.

5.1 Key Findings

Prescribers’ General Opinions about DDIs

Although the present study focused only on the interactions between prescription drugs, it should be recognized that many over-the-counter (OTC) medicines and complementary and alternative medicines (CAM) have interactions with prescription drugs and may cause serious clinical consequences (Honig and Gillespie 1995; Izzo and Ernst 2001). For example, when combined with serotonin reuptake inhibitors, St. John's wort can cause serotonin syndrome, where the elevations of central nervous system serotonin reach potentially fatal levels (Izzo 2004). The present study found that prescribers asked their patients about the use of OTC and CAM products less frequently than the use of prescription drugs. Previous studies have also demonstrated a lack of communication between doctors and patients regarding the use of these products. A study conducted at family practice and general medicine clinics found that although 57% of the patients reported using OTC medications, only during 37% of the encounters did physicians ask
questions about OTC use (Sleath et al. 2001b). In the same study, about 18% of the patients reported using alternative therapies, whereas only during 3.4% of the encounters did physicians ask questions about the therapies (Sleath et al. 2001a). Given the increasing use of OTC and CAM products, prescribers need to be aware of and take into account the risk of OTC-Rx or CAM-Rx drug interactions when prescribing. Because communication should be two-way, patients should also be educated and encouraged to proactively provide information about their self-medicating use of OTC and CAM products to their prescribers and pharmacists.

Prescribers’ Recognition of Drug-Drug Interaction

Despite the concern about discrepancies in the severity ratings and listing of DDIs (Fulda et al. 2000; Abarca et al. 2004; Chao and Maibach 2005), the clinical importance of the interacting drug combinations selected in the test of this study was verified through a rigorous review process (Malone et al. 2004). In this study it is clear that prescribers did not recognize all these potentially harmful DDIs. Although four interacting drug pairs were “contraindicated”, only sildenafil-isosorbide mononitrate was correctly classified by the majority (80.7%) of the prescribers. Another contraindicated drug pair was alprazolam and itraconazole; its low recognition rate (21.3%) helps to explain the high prevalence of the co-prescription of benzodiazepine and azole antifungal drugs that was shown in a claims database analysis (Malone et al. 2005). Even if one argued that the drug combinations classified as “contraindicated” could be used under monitoring and considered prescribers choosing either “contraindicated” or “use with monitoring” to
be correct, a significant proportion of prescribers (14.0% to 47.9%) was still not sure if there was an interaction.

Because of different drug pair selection, results of the present study may not be directly comparable to those of a previous similar study (Glassman et al. 2002). Nevertheless, a few common findings are noteworthy. Among the DDIs selected for the knowledge tests, sildenafil-isosorbide nitrate was the most highly recognized one in both studies. Sildenafil could increase the hypotensive effects of nitrates and cause adverse events such as acute myocardial infarction or even death (Malone et al. 2005). It is worrisome that still a considerable proportion of health care providers were not sure about this DDI (28% in the study by Glassman et al. and 15.4% in this study) (Glassman et al. 2002). In a follow-up study, Glassman and colleagues found that the proportion of clinicians who correctly classified sildenafil-isosorbide nitrate as contraindicated increased to 82% (Glassman et al. 2006), which is similar to the proportion reported in the present study. Consistent with their findings (Glassman et al. 2002), in the present study, on average less than 50% of the drug pairs were correctly classified, which indicated prescribers’ insufficient DDI knowledge, even though some of the DDIs selected involved commonly prescribed medications. The generally poorer recognition of DDIs found in the present study was probably a result of the restriction from using drug references when answering, whereas clinicians were allowed to consult reference materials in the previous study (Glassman et al. 2002).

With the aging of the population and the increasing complexity of medication regimens, the risk of DDIs is likely to become a growing problem. Because the number of
interacting drug combinations is enormous and growing, it is impossible to ask prescribers to be familiar with all DDIs. The suboptimal recognition rate of DDIs observed in this study demonstrates the necessity of DDI information sources for prescribers. Whenever the prescriber is not sure whether the drug combinations may have an interaction, he/she needs to have an easily accessible reference to consult.

Prescribing support systems such as PDAs and DDI alerts could also improve prescribers’ detection of potential DDIs and, consequently, have the potential to substantially reduce DDI-related adverse effects and costs. Also, several ways to avoid the occurrence of DDIs were mentioned in a previous study; while most physicians believed that increased prescriber education was very important, the authors argued that the simplest and most effective way to reduce DDIs may be to revise the formulary (Preskorn et al. 2002).

Factors Related to Prescribers’ DDI Knowledge

This study also examined the association between prescribers’ DDI knowledge scores and prescribers’ demographic and practice characteristics. Together, the predictors included in the regression model explained 21.7% of the variance in scores. Similarly, in a previous study by Glassman et al., multiple linear regression analysis was used to evaluate how prescribers’ characteristics could predict their recognition of DDIs. Although the categorization of several characteristics was different between their study and the present study, most of the predictors in their regression model were included in this study: gender, workload, specialty, practice site, weekly prescription volume, and provider type. Additionally, Glassman and colleagues included age and employment
status (i.e., full time or part time), whereas several characteristics regarding respondents’ prescribing practice were included in the present study. Both studies identified several predictors that have relationship to knowledge of DDIs. Glassman and colleagues found that nonmedical specialists correctly categorized fewer DDIs than general internists. Similarly, in the present study, compared to prescribers in general or family practice, specialists in psychiatry/neurology, surgery, obstetrics/gynecology, pediatrics, other specialty areas, and cardiology had a lower DDI knowledge score, whereas prescribers in internal medicine other than cardiology and those in emergency medicine had a score comparable to general / family practitioners. The findings may reflect the fact that prescribers are more familiar with the DDIs involving the drugs that they more frequently prescribe. Because prescribers in family practice, internal medicine, and emergency medicine are more likely to see patients with a variety of diseases, these prescribers have more opportunities to prescribe medications from a variety of therapeutic categories. On the other hand, specialists usually prescribe medications of certain categories within their specialty area, so in general they are not aware of as many DDIs as general / family practitioners.

Another predictor for prescribers’ DDI knowledge is noteworthy. Glassman and colleagues found that younger clinicians recognized more DDIs than older clinicians (Glassman et al. 2002). The result may be due to age-related memory loss or more likely, the lack or insufficiency of continuing medical education on DDIs. In the present study, however, the negative association between DDI knowledge scores and years of experience in prescribing medicines was not statistically significant ($p = 0.08$).
This study found that prescribers who had seen a patient harmed by a DDI had a higher DDI knowledge score that those who had not. These prescribers may have a better DDI knowledge because they realized the potential harm and spent more time educating themselves about DDIs. This study also revealed that the prescribers whose drug selections were affected by the risk of DDIs “very much” scored higher than those who reported that their prescribing was affected by the risk “a little” or “not at all”. The finding may be explained in two ways. The prescribers may have thought more about the risk of DDIs when prescribing because they knew a large number of DDIs and their associated adverse effects. Another explanation might be that the prescribers were more likely to seek out DDI information and thusly had more knowledge because they were more concerned about the risk when prescribing.

As revealed by a bivariate analysis, another factor found to be associated with the DDI knowledge score was the sources where prescribers obtained DDI information. The result of this study indicated that prescribers who consulted electronic references or computerized alert systems had a higher DDI knowledge score than those who consulted pharmacists. This association may be confounded by prescribers’ age. As indicated by a further analysis, on average, those who consulted pharmacists for DDI information had more prescribing experience, which indicated that they were probably older than those who consulted electronic references \((p <0.05)\). Future research with a larger sample size is needed to examine the relationship between information sources and prescribers’ DDI knowledge while controlling for potential confounders.

The unexplained variance of the regression model suggested the potential impact of
factors that were not controlled for. One potential predictor for prescribers’ DDI knowledge that was missing was the case-mix of the prescribers’ patients. Prescribers may have scored high on the test because they often had patients who needed to be treated with the medications that were included in the test. Also, the prescribers whose patients were mostly older adults may have more opportunities to prescribe multiple drugs during one encounter. These prescribers could have achieved a higher test score because they were required to pay more attention to and more frequently obtain information about DDIs. Unfortunately, in this study, the case-mix information was not available, so this factor was not adjusted for in the analysis. Future research that examines the determinants of prescribers’ DDI knowledge needs to take case-mix into account.

Both two-sample t-test and multiple regression analysis indicated that cases and controls did not differ in the DDI knowledge scores. A post-hoc power analysis was performed with an alpha value of 0.05. The power to detect a difference of 0.34 logit (i.e., 0.2 standard deviations) in mean knowledge scores was about 0.87. The sample size obtained in this study seemed to be large enough to detect a small different between the two groups if it had existed. In addition, it was found that cases and controls were equally likely to correctly categorize the DDI of interest. The findings suggest that the history of prescribing an interacting drug combination did not indicate that the prescriber was not aware of the DDI, let alone a prescriber’s general DDI knowledge. A likely explanation for the result is the potentially unreliable differentiation between cases and controls. The claims database may not have captured the interacting drug combination
prescribed by the controls outside the study period, so some prescribers in the control group may actually be unaware of the DDI of interest. Conversely, some prescribers in the case group may actually be aware of the DDI of interest. The cases may have prescribed a medication that could interact with a drug that the patient had been prescribed because the prescribers did not know about the existing drug. Another explanation may be that the prescriber had prescribed the drug combination with careful monitoring or the patient had been on the drug combination previously without adverse effects. The study results also indicated that even though a prescriber in the case group prescribed the interacting drug combination because he/she was unaware of that particular DDI, it did not imply that the prescriber would have little general DDI knowledge.

Prescribers’ Sources of DDI Information

As stated previously, it is impossible to ask prescribers to remember all DDIs. However, prescribers do need to know where to obtain DDI information and how to make the best use of the source. There are many sources available. Similar to the findings of a recent survey of VA prescribers (Ko et al. 2007), the present study found that when prescribers needed to learn more about DDIs, most of them consulted electronic references (e.g., PDAs and the Internet). The VA study found that pharmacists were equally likely to be consulted by prescribers as electronic references (each reported by about half of the respondents), whereas a lower proportion of the prescribers in the present study (14.2%) reported consulting pharmacists for DDI information. However,
more than two-thirds of the respondents reported that they were informed of their patients’ potential exposure to DDIs by pharmacists. The findings confirm the important role pharmacists play in preventing the risks of DDIs.

Based on the usefulness scores calculated by the IRT analysis, among the four different sources, DDI information provided by computerized alert systems was considered least useful. The Scheffe test indicated that the difference in the usefulness scores between “other” sources and computerized alert systems was statistically significant. Among the prescribers who were informed of their patients’ potential exposure to DDIs by “other” sources and specified what the source was, half reported that they found out about the DDIs themselves. When prescribing, these prescribers probably looked for information about DDIs themselves rather than getting informed by other sources. Because the information was specific to the patient, the information was usually considered useful by the prescribers. However, the limited sample size of this prescriber group warrants caution in the interpretation of the results. The reason that the DDI information provided by computerized DDI alerts was considered least useful is discussed in the following section.

Prescribers’ Opinions about Computerized DDI Alerts

Despite their effectiveness in preventing DDIs (Halkin et al. 2001), computerized DDI alerts are not commonly used in the current health care system. In this study, the proportion of the prescribers who reported using a CPOE system that provided DDI alerts was 11.5% and 10.2% in the national and Arizona samples, respectively. Based on the
responses of this small number of prescribers (n = 33), DDI alerts were useful tools in prescribing but there were still abundant opportunities for improvements. Similarly, previous studies suggested that users of DDI alert systems had both positive and negative views of them (Glassman et al. 2002; Magnus et al. 2002a; Abarca et al. 2006b; Glassman et al. 2006; Ko et al. 2007).

Current DDI alert systems in the US have been shown to have certain deficiencies. In this study, most respondents liked to see a greater distinction between important and less important DDIs, and most respondents agreed that it should be more difficult to override alerts for potentially lethal interactions. In addition, more than three-fourths of the respondents agreed that the alerts were sometimes not applicable or relevant to their patients. The findings were consistent with those reported in previous surveys of prescribers and pharmacists (Magnus et al. 2002a; Ko et al. 2007). Other researchers have also raised the concern about the poor relevance and specificity of DDI alerts (Glassman et al. 2002; Magnus et al. 2002a). About half of the VA clinicians surveyed in a previous study reported that too many non-relevant alerts limited use of the alerts (Glassman et al. 2002). Given the poor relevance of the alerts, it was not surprising to find that most of them were overridden (Payne et al. 2002; Weingart et al. 2003). In addition, too many irrelevant and insignificant alerts may induce “alert fatigue” and make prescribers miss truly important ones (Peterson and Bates 2001). Other suggestions for improvements included providing management options and showing the alerts only once during the order entry process (Ko et al. 2007). In summary, the findings suggest that the alert systems need to be better designed to provide more relevant information and to
improve their clinical utility.

**Application of Item Response Theory**

There were two scales developed by IRT methods in this study: prescribers’ DDI knowledge and prescribers’ attitudes towards the usefulness of DDI information. The Rasch model and RSM were used to develop the scales. These two one-parameter models were also the most commonly-used ones in previous studies assessing knowledge and attitudes in health sciences. IRT analysis indicated that, after item re-scoring and response category collapsing, all items appeared to have acceptable fit statistics within predetermined criteria. Fit statistics can be used to identify items with unexpected responses or problems such as ambiguous or negative wording. The satisfactory fit statistics in this study suggested good data-model-fit and the unidimensionality of the scales. Considering the ratio of respondents to items, it was not surprising to find that the item reliability was close to one for both scales, whereas the person reliability was medium (0.76 and 0.61). Because of the need to shorten prescribers’ time in responding, the number of items was limited in both measures. Person reliability would have been higher if more test items targeting the ability of the respondents had been included in the evaluation.

Compared to CTT, IRT can produce additional information about the psychometric properties of tests. For example, the item-person map enables researchers to easily see the relative difficulty of the items and how well the examinees performed on those items. The position of the items on the map is in the order of item difficulty estimates.
Although the order is identical to that simply based on the percentage of prescribers who correctly answer the item, distances on the scale (i.e., the vertical line on the map) can be interpreted as equal over the full range of the scale due to its interval properties. A visual inspection of the person-item map of the DDI knowledge test in this study suggested that in general, the items were well separated in difficulty and well targeted the prescribers’ DDI knowledge levels. Nevertheless, future refinements with additional items that targeted prescribers with little DDI knowledge (i.e., items with low difficulty) would help distinguish these prescribers. Also, items located on the top of the map, i.e., those DDIs that were less likely to be detected by prescribers, could be the emphasis of future educational interventions for prescribers.

For the usefulness assessment of prescribers’ usual DDI information sources, the difference in raw rating scores of individual items helped compare prescribers’ attitudes towards different sources on various aspects. ANOVA suggested that the DDI information provided by the four sources differed in terms of relevance and future usefulness. With the use of RSM, the five usefulness assessment items together constituted an interval scale and a score was calculated for each respondent that indicated prescribers’ attitudes towards the overall usefulness of the information. A higher score suggested that the prescribers more frequently considered the information useful. Also, the item difficulty estimates obtained from the RSM indicated the relative frequency that the information met the usefulness assessment items. Such information may help identify the features of DDI information that need to be improved.

Because IRT-developed scales have psychometrically-proven interval scale properties
(Streiner and Norman 2003), researchers may apply parametric tests without violating the assumption of interval scale (Cella and Chang 2000). In addition, the interval property of the scale allows meaningful and convenient interpretation of the difference in the scores calculated. As such, the 1-PL IRT analysis is currently the preferred method for Likert scale-type of items (van Alphen et al. 1994). In this study, for example, the investigator felt more comfortable applying statistical tests, such as t-test and regression, to the scores derived from IRT analysis than to raw scores (i.e., the summation of rating scores or the number of correctly categorized drug pairs).

This study provides an example of applying IRT analysis to knowledge and attitude data related to DDIs. In health sciences, although psychological measurement is commonly seen, relatively few researchers are aware of and have applied IRT in their studies. Given the ability of IRT to provide greater insights of test properties and address certain limitations of CTT, researchers need to familiarize themselves with and consider applying this alternative approach to the development, refinement, and analysis of scales.

5.2 Recommendations for Future Research

As reported by the respondents in this study, DDIs were expressed as having the potential to actually cause harm. Approximately three-fourths of the respondents reported that they had seen a DDI that caused temporary or permanent harm to the patient. In the literature, most studies of DDI rates only examined the prevalence of interacting drug combinations in prescriptions, but little is known about the occurrence and the
severity of any adverse consequences that were attributable to these potential DDIs. In addition, the economic impact of adverse events caused by DDIs is unknown. Future studies are needed to fill the gap of this knowledge, which could facilitate the cost-benefit analysis of DDI-reduction interventions. Also, more research needs to be conducted to compare the effectiveness of various approaches to reducing the occurrence of DDIs that have been proposed in previous studies.

Despite the satisfactory model-data-fit of the two scales developed in this study, the psychometric properties of the scales should continue to be evaluated in all future applications. Also, refinements of the measures are needed. Although increasing the number of items in the measures could improve the person reliability, prescribers’ time in responding would also be prolonged, which is likely to lower the response rate. One way to obtain precise estimates of examinees’ knowledge or attitudes without using too many items is to apply computerized adaptive testing (CAT), which can be developed based on IRT. The major advantage of CAT is its efficiency. By using CAT, the examinee only has to answer a small set of items that are tailored to the level of his / her knowledge or attitudes. As such, significantly less time is needed to administer a CAT than a fixed-item test because fewer items are needed to achieve an acceptable precision of estimates. In addition, assuming the item bank is large enough, CAT could prevent memory effect when the test is administered to the same prescriber more than once. In spite of the advantages of using CAT to test prescribers’ knowledge or attitudes, there are challenges as well. The cost and level of technical expertise required to develop a CAT is high, and it is difficult, if not impossible, to administer a CAT through commonly-used
survey methods, such as mail and telephone surveys. Future work needs to be done to develop the CAT version of the scales developed in this study and to evaluate its practical use in health science research.

An understanding of the determinants of prescribers’ ability to recognize DDIs could help identify the prescribers who could be targets of educational intervention on the knowledge of DDIs. This study examined the association between prescribers’ DDI knowledge scores and the characteristics of prescribers’ demographics and practice. Although more factors were examined in this study than previous research, it is likely that a few potential determinants, such as case-mix, were not included in the analysis. It is important for future studies to replicate the present study and confirm the findings. In addition, the association between other potential factors and prescribers’ DDI knowledge needs to be assessed in future research. Due to the limited sample size for the examination of the relationship between information sources and prescribers’ DDI knowledge, potential confounders could not be controlled for in this study. Future research with a larger sample size is needed to further examine the relationship and address the concern of potential confounders. In addition, future prospective studies could improve our understanding of the causative impact of different sources on prescribers’ DDI knowledge; such information would be useful for educational intervention development.

5.3 Limitations

A primary limitation of this research is the limited generalizability of the study results.
Despite the efforts made in the development and distribution of the survey, the response rate achieved was low. No sampling weights were applied to adjust for the unequal probability of sample selection. As such, the study results may not be generalizable to all national or Arizona prescribers. Selection bias is also a limitation of this study because it was possible that those who were more knowledgeable of DDIs or interested in DDI-related issues were more likely to return the questionnaire. Due to the limited information about non-respondents, it was difficult to assess how representative the respondents were. Nevertheless, with the data available it was found that the respondents and non-respondents did not differ in prescription volume or in the proportion of cases and controls. Another limitation is the potentially unreliable differentiation between cases and controls. Prescribers were divided into the case and control groups depending on whether they had prescribed a DDI during the study period. The prescribers in the control cohort may have prescribed a DDI before or after that time period, or the DDI prescribed may not have been captured by the prescription claim database used in the study.

One limitation of using mail survey is that it is impossible to know the conditions under which a respondent completed the questionnaire. Although it was clearly stated in the questionnaire that the prescriber needed to answer the DDI knowledge test items without the use of drug references, it is conceivable that respondents may have consulted an information source while answering these questions. As a result of the self-administration and self-report design of the survey, the accuracy of reported demographic and practice characteristics cannot be assessed. However, compared to
face-to-face interviews, the use of a mail survey is more likely to obtain accurate data because social desirability bias may be reduced or prevented. Also, due to the cross-sectional and non-experimental nature of the data collected, the associations examined in this study were not necessarily causative.

With regard to the limitations of the survey questionnaire, first, because there is no agreement on the listing and contraindication/monitoring classification of DDIs in the literature, the key to the knowledge test used for the scoring may not be agreed upon by all clinicians. Some DDIs classified as “contraindicated” may be “used under careful monitoring” if the patient has tolerated the DDI for a period of time and no adverse outcome has occurred. That said, the test key was reviewed and approved by an expert group who developed the original 25 DDI list, so there was a clinical rationale for each DDI classification. In addition, based on the predetermined criteria, none of the test items misfitted, which indicated that the respondents generally agreed with the classification. Second, in order to reduce respondents’ burden and increase the response rate, the length of the questionnaire was limited. Although it would be desirable to have more drug pairs in the test, this needs to offset by the need to keep the respondents’ time answering at a minimum. For items assessing the usefulness of DDI information sources, considering the ratio of respondents to items, five items may have been insufficient to obtain a reliable estimate for the prescriber’s perception of usefulness. However, compared to dichotomous-response items that could have been used, these five polytomous-response items provided more reliable estimates and more information about the usefulness of various information sources as perceived by the prescribers. Finally, it
was likely that factors associated with prescribers’ DDI knowledge were not assessed in the questionnaire. Future research is needed to examine the potential impact of these factors, such as case-mix, on the outcome measures of this study.

5.4 Conclusions

This study assessed a national sample of prescribers’ ability to recognize clinically significant drug interactions. On average, less than half of the drug-drug pairs were correctly classified by the respondents. Study results also indicated that most prescribers went to PDAs (25.9% of the respondents) or printed materials (24.1%) to learn more about DDIs, whereas most prescribers (68.4%) were usually informed about their patients’ potential DDIs by pharmacists. In general, most prescribers considered the DDI information provided by their usual source to be often useful in future prescribing and sufficient for them to manage the interaction.

In conclusion, this study suggests that prescribers may have insufficient ability to recognize clinically significant DDIs without using reference materials, which indicates the necessity and potential influence of prescribing support systems in reducing DDIs and, consequently, drug-related morbidity and mortality. This study also investigated how prescribers are informed of their patients’ potential exposure to DDIs and the relative usefulness of these information sources. In addition, this study presents an application of IRT analysis to knowledge and attitude measurement in health science research.
APPENDIX A

NATIONAL PRESCRIBER DDI SURVEY QUESTIONNAIRE-SHORT VERSION
Please provide us with your opinion about drug safety and drug interactions and some characteristics of your practice. Unless specified otherwise, please provide the single best answer to each question.

1. To what extent does the risk for a drug interaction affect your selection of a drug product?
   - Not at all
   - A little
   - Somewhat
   - Very much

2. Have you ever seen a patient who had a drug interaction that caused temporary or permanent harm?
   - Yes
   - No

3. In your opinion, which occurs more frequently? An interaction caused by drugs that are prescribed by:
   - The same prescriber
   - OR
   - Two different prescribers

4. On average, how many patients do you see per workday? ________

5. On average, how many hours a week do you see patients? ________ hours

6. How many years have you been a practicing licensed prescriber? ________ years

7. What is the most common method you use for prescribing medications?
   - Hand-written
   - Telephone prescription
   - Electronic prescription

8. When on-call, do you provide care for patients outside your usual panel of patients?
   - Yes
   - No
   - Not applicable

9. How frequently do you ask patients about their use of the following products?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Usually</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. OTC products</td>
<td></td>
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<tr>
<td>b. Prescription drugs</td>
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</tr>
<tr>
<td>c. Complimentary/alternative products</td>
<td></td>
<td></td>
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</tbody>
</table>

10. Do you practice in more than one location?
    - Yes
    - No

11. Which setting best describes the type of office/practice where you see patients most of the time (i.e., your primary practice site)? (Choose one only)
   - Office-based practice (solo)
   - Office-based practice (group)
   - Hospital-based clinic
   - Hospital acute care
   - Urgent Care
   - Other: ____________

12. Do you use electronic medical records at your primary practice site?
    - Yes
    - No
We are interested in the ability of prescribers to identify potential drug interactions without the use of drug references. Please evaluate the potential for the following drug pairs to interact. Please check the box that best describes the appropriate use of the two drugs in the same patient.

<table>
<thead>
<tr>
<th>Drug Pair</th>
<th>Should not be used together (contraindicated)</th>
<th>May be used together but with monitoring</th>
<th>No interaction</th>
<th>Not sure</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Coumadin® and Tagamet® (warfarin and cimetidine)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b. Viagra® and Wellbutrin® (sildenafil and bupropion)</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>c. Rheumatrex® and Bactrim DS® (methotrexate and trimethoprim-sulfamethoxazole)</td>
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<tr>
<td>d. Neoral® and Rifadin® (cyclosporine and rifampin)</td>
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<tr>
<td>e. Coumadin® and Calan® (warfarin and verapamil)</td>
<td>☐</td>
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<tr>
<td>f. Valtrex® and Zocor® (valacyclovir and simvastatin)</td>
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<tr>
<td>g. Amoxicillin® and Tylenol #3® (amoxicillin and APAP w/codeine)</td>
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<tr>
<td>h. Tenormin® and Zantac® (atenolol and ranitidine)</td>
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<td>i. Lenoxin® and Blazin® (digoxin and clarithromycin)</td>
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<td>j. Micronase® and Posamax® (glyburide and amlodipine)</td>
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<tr>
<td>k. Viagra® and Indur® (sildenafil and isosorbide dinitrate)</td>
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<td>l. Ambien® and Ditropan® (zolpidem and oxybutynin)</td>
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<td>m. Symmetrel® and Atrovent® (amantadine and ipratropium)</td>
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<tr>
<td>n. Xanax® and Spiranox® (alprazolam and triamterene)</td>
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<td>o. DDI pair of interest (drug1 and drug2)</td>
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</table>

Finally, the following questions will provide us some general information about YOU. Please provide the single best answer to each question.

13. What is your sex? ☐ Male ☐ Female

14. What is your profession?
   ☐ Physician ☐ Nurse practitioner ☐ Physician Assistant
   ☐ Dentist ☐ Other, please specify ____________________________

15. Please indicate your specialty area: ______________________________

16. Do you have national board certification?
   ☐ No ☐ Yes, please describe ________________________________

Thank You For Your Participation. Further instructions on mailing.
APPENDIX B

NATIONAL PRESCRIBER DDI SURVEY QUESTIONNAIRE-LONG VERSION
Please provide us with your opinion about drug safety and drug interactions and some characteristics of your practice. Unless specified otherwise, please provide the single best answer to each question.

1. To what extent does the risk for a drug interaction affect your selection of a drug product?
   - Not at all  
   - A little  
   - Somewhat  
   - Very much

2. Have you ever seen a patient who had a drug interaction that caused temporary or permanent harm?
   - Yes  
   - No

3. In your opinion, which occurs more frequently? An interaction caused by drugs that are prescribed by:
   - The same prescriber  
   - Two different prescribers

4. On average, how many patients do you see per work day? ________

5. On average, how many hours a week do you see patients? ________ hours

6. How many years have you been a practicing licensed prescriber? ________ years

7. What is the most common method you use for prescribing medications?
   - Hand-written prescription  
   - Telephone prescription  
   - Electronic prescription

8. When on-call, do you provide care for patients outside your usual panel of patients?
   - Yes  
   - No  
   - Not applicable

9. How frequently do you ask patients about their use of the following products?

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10. Do you practice in more than one location?
    - Yes  
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11. Which setting best describes the type of office/d clinic where you see patients most of the time (i.e., your primary practice site)? (Choose one only)
   - Office-based practice (solo)  
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   - Hospital-based clinic  
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   - Urgent Care  
   - Other: ______________________

12. Do you use electronic medical records at your primary practice site?
    - Yes  
    - No
We are interested in the ability of prescribers to identify potential drug interactions without the use of drug references. Please evaluate the potential for the following drug pairs to interact. Please check the box that best describes the appropriate use of the two drugs in the same patient.

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<td>c. Rheumatrex® and Bactrim DS®</td>
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<td>(methotrexate and trimethoprim-</td>
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<td>i. Loprin® and Blaxin®</td>
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<td>(diclofenac and clindamycin)</td>
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<td>j. Micronase® and Posaconzol®</td>
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<td>(glyburide and alendronate)</td>
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<tr>
<td>k. Viagra® and Imdur®</td>
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<tr>
<td>n. Xanax® and Sporanoz®</td>
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<tr>
<td>(alprazolam and itraconazole)</td>
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<tr>
<td>o. ODI pair of interest</td>
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</tr>
<tr>
<td>(drug 1 and drug 2)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Please provide us with information about drug interactions and preventing them.

13. When you want to learn more about an interaction, what reference/person do you use? (choose only one)

- ☐ Package insert
- ☐ Computerized alert system
- ☐ Pharmacist
- ☐ Printed materials
- ☐ Personal digital assistant (PDA)
- ☐ Internet
- ☐ Other:

14. When one of your patients is about to be exposed to a potential drug interaction, who usually informs you that the interaction may be present?

- ☐ Pharmacist
- ☐ Computerized alert system
- ☐ Personal digital assistant (PDA)
- ☐ Other:

Please answer questions 13 to 19 based on your opinions concerning your usual source of drug-drug interaction information.

15. How often does the drug interaction information change your initial prescribing decisions?

- ☐ Never
- ☐ Seldom
- ☐ Sometimes
- ☐ Usually
- ☐ Always
18. How often is the drug interaction information new to you?
   - Never
   - Somewhat
   - Sometimes
   - Usually
   - Always

17. How often is the drug interaction information relevant to the patient?
   - Never
   - Somewhat
   - Sometimes
   - Usually
   - Always

16. Is the drug interaction information sufficient for you to manage the interaction?
   - Never
   - Somewhat
   - Sometimes
   - Usually
   - Always

15. How often is the drug interaction information useful to you in future prescribing?
   - Never
   - Somewhat
   - Sometimes
   - Usually
   - Always

20. Do you use computerized physician order entry (CPOE) for medication orders in your primary practice setting?
   - Yes
   - No (If No, go to Question 29)

21. Does your order entry system provide drug interaction alerts?
   - Yes
   - No (If No, go to Question 29)

22. Anecdotal reports suggest that physicians believe that they sometimes override interaction alerts without properly checking them. How often does this happen to you?
   - Never
   - Somewhat
   - Sometimes
   - Usually
   - Always

23. Drug interaction alerts are a useful tool in prescribing:
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

24. Drug interaction alert systems are good at alerting me to significant interactions:
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

25. There should be a greater distinction between important and less important interactions:
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

26. It should be more difficult to override alerts for potentially lethal interactions:
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

27. The information on the drug interaction alert system is not always reliable:
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

28. How do you rate your computer skills?
   - Strongly disagree
   - Disagree
   - Neutral
   - Agree
   - Strongly agree

Finally, the following questions will provide us some general information about YOU. Please provide the single best answer to each question.

20. What is your sex?
   - Male
   - Female

21. What is your profession?
   - Physician
   - Nurse practitioner
   - Physician Assistant
   - Dentist
   - Other, please specify____________________

31. Please indicate your specialty area: ________________________________

32. Do you have national board certification?
   - No
   - Yes, please describe________________________
APPENDIX C

ARIZONA PRESCRIBER DDI SURVEY QUESTIONNAIRE
SECTION 1. Please provide us with your opinion about drug safety and drug interactions and some characteristics of your practice. Unless specified otherwise, please provide the single best answer to each question.

1. To what extent does the risk for a drug interaction affect your selection of a drug product?
   □ Not at all □ A little □ Somewhat □ Very much

2. Have you ever seen a patient who had a drug interaction that caused temporary or permanent harm?
   □ Yes □ No

3. In your opinion, which occurs more frequently? An interaction caused by drugs that are prescribed by:
   □ The same prescriber □ OR □ Two different prescribers

4. On average, how many patients do you see per work day? _________

5. On average, how many hours a week do you see patients? _________ hours

6. How many years have you been a practicing licensed prescriber? _________ years

7. What is the most common method you use for prescribing medications?
   □ Hand-written prescription order □ Telephone prescription order □ Electronic prescription order

8. When on-call, do you provide care for patients outside your usual panel of patients?
   □ Yes □ No □ Not applicable

9. How frequently do you ask patients about their use of the following products?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Usually</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. OTC products</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Prescription drugs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>c. Complimentary/alternative products</td>
<td></td>
<td></td>
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</tbody>
</table>

10. Do you practice in more than one location?
    □ Yes □ No

11. Which setting best describes the type of office/clinic where you see patients most of the time (i.e., your primary practice site)? (Choose one only)
    □ Office-based practice (sole) □ Office-based practice (group) □ Hospital-based clinic
    □ Hospital acute care □ Urgent Care □ Other _________

12. Do you use electronic medical records at your primary practice site?
    □ Yes □ No
We are interested in the ability of prescribers to identify potential drug interactions without the use of drug references. Please evaluate the potential for the following drug pairs to interact. Please check the box that best describes the appropriate use of the two drugs in the same patient.

<table>
<thead>
<tr>
<th>Drug Pairs</th>
<th>Should not be used together (contraindicated)</th>
<th>May be used together but with monitoring</th>
<th>No interaction</th>
<th>Not sure</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Coumadin® and Tagamet® (warfarin and cimetidine)</td>
<td>☐</td>
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<td>☐</td>
<td>☐</td>
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<tr>
<td>b. Viagra® and Wellbutrin® (sildenafil and bupropion)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tr>
<tr>
<td>c. Rheumatrex® and Bactrim DS® (methotrexate and trimethoprim-sulfamethoxazole)</td>
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<td>☐</td>
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<tr>
<td>d. Neoral® and Rifadin® (cycloserine and rifampin)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>e. Coumadin® and Calian® (warfarin and verapamil)</td>
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<tr>
<td>f. Valtrex® and Zocor® (valacyclovir and simvastatin)</td>
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<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>g. Amoxicillin® and Tylenol® #3 (amoxicillin and APAP w/ codeine)</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>h. Tenormin® and Zantac® (atenolol and ranitidine)</td>
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<tr>
<td>i. Lomoxin® and Biaxin® (doxycycline and clarithromycin)</td>
<td>☐</td>
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<tr>
<td>j. Micromase® and Fosamax® (gliburide and alendronate)</td>
<td>☐</td>
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<td>k. Viagra® and Imdur® (sildenafil and isosorbide dinitrate)</td>
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<td>☐</td>
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<td>l. Ambien® and Ditropan® (zolpidem and oxybutynin)</td>
<td>☐</td>
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<tr>
<td>m. Symmetrel® and Atrovent® (amantadine and ipratropium)</td>
<td>☐</td>
<td>☐</td>
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<td>n. Xanax® and Sporanoxx® (alprazolam and itraconazole)</td>
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<tr>
<td>o. DDI pair of interest (drug 1 and drug 2)</td>
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</tbody>
</table>

Please provide us with information about drug interactions and preventing them.

13. When you want to learn more about an interaction, what reference/person do you use? [Choose only one]
   - Package insert
   - Computerized alert system
   - Pharmacist
   - Printed materials
   - Personal digital assistant (FDA)
   - Internet
   - Other: ________________________________

14. When one of your patients is about to be exposed to a potential drug interaction, who usually informs you that the interaction may be present?
   - Pharmacist
   - Computerized alert system
   - Personal digital assistant (FDA)
   - Other: ________________________________
SECTION II. Please answer questions 1 to 5 based on your opinions concerning your usual source of drug-drug interaction information.

1. How often does the drug interaction information change your initial prescribing decisions?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always

2. How often is the drug interaction information new to you?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always

3. How often is the drug interaction information relevant to the patient?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always

4. Is the drug interaction information sufficient for you to manage the interaction?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always

5. How often is the drug interaction information useful to you in future prescribing?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always

SECTION III. The following questions will provide us some general information about YOU. Please provide the single best answer to each question.

1. What is your sex?  □ Male  □ Female

2. What is your profession?
   - □ Physician  □ Nurse Practitioner  □ Physician Assistant
   - □ Dentist  □ Other, please specify________________________

3. Please indicate your specialty area: ________________________________

4. Do you have national board certification?
   - □ No  □ Yes, please describe__________________________________

SECTION IV. Finally, please answer the following questions that pertain to your opinions about computerized DRUG-DRUG INTERACTION (DDI) alerts.

1. Do you use computerized physician order entry (CPOE) for medication orders in your primary practice setting?
   - □ Yes  □ No (if No, please stop here)

2. What is the name of the CPOE system that you are currently using? ___________________________

3. Does your order entry system provide drug interaction alerts?
   - □ Yes  □ No (if No, please stop here)

4. Anecdotal reports suggest that physicians believe that they sometimes override interaction alerts without properly checking them. How often does this happen to you?
   - Never  □ Seldom  □ Sometimes  □ Usually  □ Always
6. Drug interaction alerts are a useful tool in prescribing.
   - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

6. Drug interaction alert systems are good at alerting me to significant interactions.
   - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

7. There should be a greater distinction between important and less important interactions.
   - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

8. It should be more difficult to override alerts for potentially lethal interactions.
   - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

9. The information on the drug interaction alert system is not always reliable.
   - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

10. The information provided by the DDI alert system is just about all I need.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

11. DDI alerts frequently provide me with information that I already know.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

12. DDI alert system enables me to prescribe more safely.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

13. I feel confident in the computer's ability to provide me with meaningful DDI alerts.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

14. DDI alerts are sometimes not applicable/relevant to the patient.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

15. I am satisfied with the format in which DDI alerts are provided.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

16. DDI alerts are annoying.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

17. Overall, I am satisfied with the DDI alert system.
    - Strongly disagree  - Disagree  - Neutral  - Agree  - Strongly agree

18. How do you rate your computer skills?
    - Novice  - Below average  - Average  - Good  - Expert
APPENDIX D

COVER LETTER FOR THE 1st MAILING
Dear Dr. Doe:

The 1999 Institute of Medicine's (IOM) report on medical errors, *To Err is Human*, suggested that between 44,000 to 98,000 persons die annually from medical errors. The majority of these errors appear to be the result of a failure of the system through which we provide care. Currently, more research is needed to understand the separate components of the system at which health care is provided.

You have been randomly selected from a sample of US clinicians to provide insight into this matter. The enclosed questionnaire is designed to collect descriptive information about your practice that can be linked to drug utilization information from pharmacy benefit managers. The questionnaire will take approximately 10 minutes to complete. Your responses to our questionnaire are very important to us. Your responses will allow us to increase our understanding of the factors associated with the prevention of drug interactions and will aid society in designing safer care systems for patients.

The complete confidentiality of your responses is assured. A random identification number is printed on your questionnaire to prevent future mailings from being sent to you once you have returned the questionnaire. The identifier will also be used to link your responses with drug utilization data. There is no risk that your responses will be used in an inappropriate manner that will violate this confidentiality. Your participation is voluntary, and you may stop at any time. By returning this questionnaire, you will be providing us your consent to use your responses for research purposes. As a token of our appreciation, respondents will be entered in a drawing for one of six PalmOne LifeDrive Mobile Manager PDAs with a choice of select drug information software (e.g., A to Z Drug Facts, FactsMD: Drug Information Facts).

The results of this study will be made available via peer-reviewed journal. I would be happy to answer any questions you might have. You may contact me at the address printed above or by telephone at 510-626-3532. If you have any questions related to this research or your participation in the study, you may call the Human Subjects Committee at 510-626-6721. Thank you in advance for your time and valuable contribution.

Sincerely,

Raymond L. Woolsey, MD, PhD
President
Critical Path Institute
APPENDIX E

COVER LETTER FOR THE 2nd MAILING
Date

John Doe, M.D.
1234 Address Dr.
City, State XXXX-XXXX

Dear Dr. Doe,

About three weeks ago you should have received a letter and a survey from the University of Arizona seeking information about your professional practice and drug-drug interactions. We are writing you again because the study’s usefulness depends on our receiving a questionnaire from those willing to participate. If you have already returned a completed questionnaire, we thank you for your time and assistance. If you have not returned the questionnaire, please consider doing so today. For your convenience, we have enclosed another copy of it.

You have been randomly selected from a sample of US clinicians to provide insight into this matter. The enclosed questionnaire is designed to collect descriptive information about your practice that can be linked to drug utilization information from pharmacy benefit managers. The questionnaire will take approximately 10 minutes to complete. Your responses to our questionnaire are very important to us. Your responses will allow us to increase our understanding of the factors associated with the prevention of drug interactions and will aid society in designing safer care systems for patients.

The complete confidentiality of your responses is assured. A random identification number is posted on your questionnaire to prevent future mailings from being sent to you once you have returned the questionnaire. The identifier will also be used to link your responses with drug utilization data. There is no risk that your responses will be used as an inappropriate manner that will violate this confidentiality. Your participation is voluntary, and you may stop at any time. By returning this questionnaire, you will be providing us your consent to use your responses for research purposes. As a token of our appreciation, respondents will be entered in a drawing for one of six PalmOne LifeGuide Mobile Manager PDAs with a choice of select drug information software (e.g., A to Z Drug Facts, iPharm™, Drug Interaction Facts).

The results of this study will be made available via a peer-reviewed journal. It would be happy to answer any questions you might have. You may contact me at the address printed above or by telephone at 500-626-3532. If you have any questions related to this research or your participation in the study, you may call the Human Subjects Committee at 500-626-6721. Thank you in advance for your time and valuable contribution.

Sincerely,

Raymond L. Woodley, M.D., PhD
President
Critical Path Institute
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