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Effects of Off-Label Prescribing on Patient Decision Making

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EFFECTS OF OFF-LABEL PRESCRIBING ON PATIENT DECISION MAKING

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ABSTRACT

Objectives: Despite the common use of off-label prescribing in the US, no research has been conducted to understand the impact of off-label prescribing on patient decision making. This study sought to measure the impact on trust in physicians, intentions of involvement in the decision making, beliefs about the drug, and initial compliance intentions in elderly and nonelderly populations.

Methods: This study was designed to assess the effects of off-label prescribing using a 2 × 2 × 2 design. Using an online panel, 830 consumers were surveyed, 409 elderly and 421 nonelderly, using 8 different scenarios based on disease criticality, off-label use norms, and the FDA approval status of the drug for the disease for which it was prescribed. The effect on trust in the physician, intentions of involvement in decision making, beliefs about the drug, and initial compliance intentions were assessed.

Results: Off-label prescribing decreased trust in the physician, increased intentions of involvement in medical decision making, and lowered positive beliefs about the drug. There was a greater loss in physician trust when receiving an off-label prescription in a less critical disease state than when receiving an off-label prescription in a more critical disease state. The data revealed a significant loss in positive beliefs about the drug when receiving an off-label prescription compared to on-label drug in the less critical disease state. Respondents judged the physician-provided information about the drug as relevant/reliable, and this led to the creation of

positive beliefs about the drug as well as initial compliance intentions. The elderly appeared slightly more trusting of physicians and positive in their beliefs about drugs and possessed higher intentions of initial compliance.

Conclusions: Off-label prescribing can lead to deleterious effects on patients' health, including lower compliance, lower trust in the physician, and lower beliefs in the drug. Differences exist between the elderly and the nonelderly that may call for different interventions. As shown in previous research, judgments of the relevance/reliability of the information appear to filter which information is used to form beliefs about the drug and affect initial compliance intentions. This work revealed a rich area for future research.

DEDICATION

This work is dedicated to my wife, Beth, whose continued love and support have allowed me to learn, be challenged, and enjoy.

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After achieving a goal, one should be quick to look back and recognize those who enabled it. My path is full of special people with unique skills and great timing. These are people (listed in chronological order) to whom I am indebted and grateful:

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- Dr. Charles Hussey, who told me, "You don't want to be a surgeon. You want a Ph.D."
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CHAPTER I

INTRODUCTION

Off-label prescribing is the use of a prescribed medication in a manner different from that approved by the Food and Drug Administration (FDA) (Stafford 2008). In the United States, since 1962, a prescription drug must be proven safe and effective for the indications listed on its label before it is approved for marketing. Former FDA Acting Director Steven Galson stated the following about an FDA approval and its associated safety and efficacy:

> What it means when a drug is approved is that the risks are outweighed by the benefits for the indication and under the conditions that are in the label. That just means if the drug is used in the right patients, in the right way, at the right dose, and there aren't drugs that are contraindicated taken with it, that the benefits outweigh the risks. There's a lot that can go wrong that doesn't fit under that definition. But the benefits outweigh the risks for the indication and under the conditions of use that we specify when we approve drugs, and the public should feel very comfortable with the review process. (PBS 2011)

Once a product is approved by the FDA and marketed in the United States, however, physicians can legally rely on their professional judgment to use an FDA-approved product in different diseases, different aged patients, or different doses that are not approved by the FDA. This is called off-label use. Examples are:

- Different disease – an FDA-approved drug to treat blood pressure is used to treat migraine headaches

- Different patients – an FDA-approved drug to treat depression is used in children less than 12 years of age even though it was not studied in this population
- Different dose – an FDA-approved drug to treat a sinus infection is used at a higher dose than listed in the FDA-approved label.

The FDA even condones off-label use when appropriate:

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. (FDA 2011)

Off-label prescribing is rather common, especially in the therapeutic areas of oncology, psychiatry, HIV, and pediatrics (Radley et al. 2006, Peppercorn 2008, Soares 2005, Tarbarrok 2000, Bazzano 2009, Pathak et al. 2010). One study found that 80% of oncologists had used drugs off-label and approximately half of their chemotherapy use was for indications not approved by the FDA (Mortenson 1988). Despite the common occurrence of off-label prescribing, there are no US studies addressing patient attitudes or behaviors toward prescriber behavior that may significantly affect patient health. Only the opinions of parents of 51 healthy children and 43 children with renal disease (Lenk et al. 2009) have been assessed in Germany. "Knowledge about the practise of off-label use [was] generally poor in both groups. Surprisingly, this [was] also true for the parents of children with chronic disease. Nine percent of the parents of chronically ill children and 20% of the parents of healthy children would refuse treatment with an off-label drug" (p. 1743).

Although it is legal in the US for physicians to use drugs off-label, it is not legal for drug companies to market FDA-approved drugs for off-label uses. Numerous legal cases against companies promoting prescription drugs off-label have resulted in billions of dollars in settlements and fines (examples include Pfizer's settlement for $2.3 billion in 2009 after Eli Lilly was charged $1.4 billion earlier that year) (Law 2007). Off-label marketing is very different from off-label use, and this study does not address implications of off-label marketing.

The use of off-label drugs has been addressed from the viewpoints of the physician, payer, regulatory, and legal communities. However, a void exists in the literature for studies assessing US patients' attitudes toward off-label use, the perceived value of an approved FDA indication, and the patient decision making to comply with the physicians' prescribing of off-label drugs.

Medication Compliance/Adherence

Compliance is defined as the extent to which a patient takes the medication as prescribed by the health care provider. The term has been criticized because it suggests that patient involvement is passive. Adherence is also used as it suggests the addition of patient agreement with the instructions (Osterberg and Blaschke 2005, Bentley et al. 1999).

Patients can deviate from the prescriber's instructions either volitionally or nonvolitionally. When the patient makes a conscious choice to be noncompliant with the instructions is involved, the deviation is volitional (Bentley et al. 1999).

The exact path of noncompliance is rather complex, and the costs are potentially greater than $258.3 billion (Express Scripts 2010). After a review of the literature (1966 to 2002) on compliance among community-dwelling older patients, Vik et al. (2004, p. 303) found that "polypharmacy and poor patient–healthcare provider relationships (including the use of multiple

providers) may be major determinants of nonadherence among older persons, with the impact of most sociodemographic factors being negligible. There is little consensus regarding other determinants of nonadherence." The authors also report that as high as 11% of hospitalizations among older patients are attributable to nonadherence (Vik et al. 2004).

Patient Decision Making

Patient decision making is complex. Fincham and Wertheimer (1985) identified more than 250 social, economic, medical, and behavioral factors associated with noncompliance, including factors such as disease severity and criticality, that put patients at different levels of health risks. In decision making, beliefs determine intentions, which, in turn, determine actual behavior (Ajzen and Fishbein 1980).

Smith et al. (1991) proposed that beliefs are derived from information that is processed using judgments and arguments. Although their work is based on the Toulmin Model of Argumentation (Toulmin 1958), it substantially varies in two areas: (1) they propose three modules that work interactively, not sequentially, and (2) they introduced screens of relevance and reliability through which information is judged. In the first module, data are retrieved internally from memory or externally through perception. In the second module, these data are judged against the concepts of relevance and reliability to determine whether the data are worthy and applicable for argument construction. Finally, in the third module, referred to as the reasoning or argument construction, these data are transformed into beliefs.

The role of relevance and reliability judgments in belief formation has been addressed in several studies (Sewak 2002, West et al., 2004, Jalnawala and Wilkin 2004, Lobb 2007, King and Wilkin 2004). Patients have used relevance judgments to assess the utility of the information and reliability judgments to assess the dependability of pharmacists (West et al.

2004). In a consumer study of weight loss supplements, the relevance and reliability of the information were more predictive of beliefs than source credibility (King and Wilkin 2004).

The impact of physician prescribing of off-label therapies on patients' beliefs is unknown, including the effect on the physician-patient relationship and ability to exchange information which is important in the physician-patient relationship (Hall et al. 2002).

Patient Trust in Physicians and Involvement in Medical Decision Making

"Patient trust can be considered a collective good, similar to 'social capital,' that is necessary for an effective health care system" (Thom et al. 2004, p. 126). The importance of trust in medical relationships has been acknowledged in the literature dating as far back as 1927, but the concept was not "systematically analyzed or measured" (Hall et al. 2002, p. 294) until the last 20 years. The first scale was developed in 1990 (Anderson and Dedrick 1990). Since then, several teams have been working in the area (Kao et al. 1998, Hall et al. 2002, Thom et al. 1997, Thom et al. 1999, Safran et al. 1998). Each team identified five overlapping domains/dimensions consisting of fidelity, competence, honesty, confidentiality, and global trust (Greenbridge 2011). Despite efforts to identify and separate these unique dimensions, trust appears to be unidimensional; in fact, "the failure to differentiate between competence and other aspects of trust is especially notable" (Hall et al. 2002, p. 313).

It is also important to note the distinction "between interpersonal trust, which characterizes a relationship between two individuals, such as a specific physician-patient relationship, and institutional or system trust, which characterizes attitudes toward collective or social organizations" (Hall et al. 2002, p. 297). The large domain of trust seems to move beyond the individual physician. The development of scales to test trust in different health care participants (e.g., payers or insurance companies) has been valuable, as it has been found that

HMO enrollees are less likely than those in non-HMOs to express trust in their physicians (Lake et al. 1999-2000). Another study found that "disclosing the positive and negative features of incentives and increasing knowledge of these incentives does not, in the short term, reduce trust in physicians or insurers and may have a mild positive impact on trust in physicians, perhaps as a consequence of displaying candor and increasing understanding of positive features" (Hall et al. 2002, p. 197).

Trust in the medical profession has been found to be a significant predictor of self reports of many patient behaviors, including following physician treatment recommendations and willingness to rely on physicians' judgment (Trachtenberg et al. 2005, Thom et al. 1999). Researchers concluded that a "trusting physician relationship may moderate the impact of cost pressures on patients' medication adherence. More generally, addressing noncost barriers to adherence may reduce rates of cost-related medication underuse" (Piette 2005, p. 1749).

Appropriately ascribing the antecedents and determinants of trust will enable better interventions in this important and complex relationship. The importance of this connection between trust and compliance grows as physicians move from a paternalistic role to more collaborative care involving the patient in health care decisions (Hammond and Lambert 1994) and as the influence of third parties grows.

Patients' preference on involvement in their medical decision making has been measured (Say et al. 2005). Studies have found that these preferences are influenced by patients' demographic variables, their experience of illness and medical care, their diagnosis and health status, the type of decision they need to make, the amount of knowledge they have acquired about their condition, their attitude toward involvement, and the interactions and relationships they experience with health professionals. The connection with trust and involvement is also

complex and has been shown to be more closely associated with trust in the medical profession than trust in the individual physician (Trachtenberg et al. 2005).

Disease Criticality

Conditions affecting human health are not all created equal. One can expect that chapped lips may result in different attitudes and behaviors than cancer. Compliance has been shown to vary across different disease states and at times has been found to be more closely associated with the perception of risk than with the disease itself (Christensen 1978, Porter 1969). The patient desire to be involved in medical decision making can evolve within a disease state as a patient progresses (Say et al. 2005) and has been shown to exist and vary in diseases of high criticality (Levinson et al. 2005), such as cancer (Bruera et al. 2001). As with these other patient measures, the effect of off-label use may also vary across different disease states with different levels of immediate risk and magnitude of risk.

Research Questions

Given the widespread off-label use of pharmaceuticals (Radley et al. 2006, Peppercorn 2008, Soares 2005, Pathak et al. 2010), one is led to question the effect of off-label use on patient decision making. Nevertheless, the attitudes, beliefs, and behavioral intentions of patients regarding off-label use are largely unknown. Only one study, conducted in German parents, exists. This study shows the parents' general ignorance of the occurrence of the behavior as well as a concern for their children (Lenk et al. 2009). This research will address the following questions:

- What are the roles of disease criticality, FDA approval status of the prescribed drug, and the "normal" level of off-label use in beliefs formed about the prescribed drug,

level of trust in physicians, level of involvement in medical decision making, and intentions of initial compliance?

- What are the roles of relevance and reliability judgments of the physician-provided information and trust in physicians in the beliefs formed about a prescribed drug and the intentions of initial compliance?
- How do the roles of these elements differ in a population of elderly patients when compared to younger patients?

Study Significance

There are no studies of patient perceptions of off-label use publicly available. Although some studies have measured the existence of off-label use (Radley 2006, Soares 2005, Kauffman 1996, Bazzano 2009, Peppercorn 2008, Pathak et al. 2010) and the need of market participants to address and regulate off-label use (Stafford 2008, Fairman 2010), virtually nothing is known about patient views of off-label prescribing.

An estimated $258.3 billion is wasted each year in the health care system based on nonadherence with prescriptions (Express Scripts 2010). Trust in physicians is associated with patient adherence (Hall et al. 2002), yet only one small study (Lenk et al. 2009) has addressed patient attitudes and behavioral intentions regarding this common phenomenon of off-label prescribing.

Due to the importance to society of patient compliance, the frequency of off-label use within this market, and the value of trust in physician-patient relations, it is important to understand the potential effects of off-label use of pharmaceuticals in patient decision making.

CHAPTER II

LITERATURE REVIEW

Off-Label Prescribing

Studies have found that 21% of commonly used drugs are used in indications for which the FDA has not specifically approved them (Radley 2006). Up to 75% all oncology uses are not FDA approved (Soares 2005), and at least 80% of pediatric patients are prescribed products that lack an FDA approval for the use. What remains unknown is how many of the 93% of consumers who are confident about the safety and effectiveness of drugs approved for use in the United States know this (Kauffman 1996, Bazzano 2009).

Off-label use is so prevalent that physicians may not even know they are doing it. Even when the set of drugs was limited to those that physicians prescribed, they only accurately identified the FDA status of commonly used drugs and the FDA approval status of common uses 60% of the time:

> Physicians' beliefs that individual drug-indication pairs were FDA-approved were strongly correlated with the level of evidence supporting the use in question. However, a substantial minority of respondents believed that some drug-indication pairs without evidence supporting efficacy were actually FDA approved for the use in question. For example, among the 42% of physicians who prescribed quetiapine (Seroquel®) for dementia with agitation during the previous 12 months, nearly one in five (19%) erroneously believed it was FDA-approved for this use, when in fact quetiapine has never

been FDA approved for this indication and at the time of our survey carried a black-box warning for "increased risk of death compared to placebo" in elderly patients with dementia. (Chen et al. 2009)

Off-label prescribing is especially common in the therapeutic areas of oncology, psychiatry, and pediatrics (Radley et al. 2006, Peppercorn 2008, Tarbarrok 2000, Bazzano 2009, Pathak et al. 2010). Radley et al. used nationally representative data from the 2001 IMS Health National Disease and Therapeutic Index (NDTI) to classify the prescribing patterns by diagnosis for 160 commonly prescribed drugs. Each reported drug-diagnosis combination was marked as (1) Food and Drug Administration approved, (2) off-label with strong scientific support, or (3) off-label with limited or no scientific support. Multivariate analyses were unable to identify predictive characteristics of off-label drugs beyond belonging to the several drug classes that were largely known. Of the estimated 150 million off-label mentions (21% of overall use), off-label use was most common among cardiac drugs (46%, excluding antihyperlipidemic and antihypertensive agents) and anticonvulsants (46%). The greatest proportions of off-label use among specific drugs were gabapentin (83%) and amitriptyline hydrochloride (81%). An alarming finding was that 73% of off-label drug mentions had little or no scientific support.

Previous studies were less robust and focused on specific drugs or therapeutic areas such as pediatrics, oncology, and psychology. Bazzano et al. (2009) looked at outpatient pediatric visits and found that 62% included off-label prescribing. Off-label prescribing was found to be common for many therapeutic areas: 96% of cardiovascular-renal, 86% of pain, 80% of gastrointestinal, and 67% of pulmonary and dermatologic medications. Off-label prescribing was more likely in visits by children aged < 6 years, especially visits by children aged < 1 year.

Specialists were also more likely to use off-label prescribing (68% versus 59% for general pediatricians).

In oncology, 75% of rituximab administrations were for off-label use at an academic center (Kocs et al. 2003). This finding is consistent with Soares' (2005) finding that 50% to 75% of all oncology therapies are off-label. Over 80% of oncologists reported using investigational therapies for non-FDA approved uses (90% of academic oncologists and 75% of community oncologists) (Peppercorn 2008).

Pathak and colleagues (2010) explored the prescribing of second generation antipsychotics in a state Medicaid pediatric population from 2001 to 2005 and the published support for the uses. Use doubled over the time frame, yet 41.3% of new users lacked a diagnosis for which the treatment was supported by a published study.

The off-label use of drugs is so common in cancer that the American Cancer Society (2011) Web site has a section entitled, "What questions should I ask my physician about off-label drug use?" with the following guidance:

> Here are some questions you may want to ask your doctor. Start by asking if all the drugs recommended for your cancer treatment are approved for the planned use. If any of the drugs are not, you can ask:
>
> - Is there evidence to support the off-label use of this drug to treat my type of cancer?
> - Is this off-label drug likely to work better than an approved drug?
> - What are the risks and benefits of off-label treatment with this drug?
> - Will my health insurance cover off-label treatment with this drug?
> - If my treatment involves a combination of drugs and one of the drugs is being used off label, will my health insurance cover it?

Cancer is relatively unique in that many oncologists may not be aware of the FDA-approved use of the drug, but they are likely aware of its compendia listing. Compendia are often developed by expert panels that review the clinical data in support of products for particular uses. When trying to get reimbursement from payers, 90% of oncology practice managers believe they have a better chance of getting paid for their treatment decision when they base their coverage argument on compendia (Cote 2008). For oncologists, the utility of knowing the FDA-approved indication is minimized when the reality that compendia are richer resources of clinical data relative to FDA labels is combined with the fact that reimbursement is often tied to use in line with the compendia.

In the United States, since 1962, a prescription drug must be proven safe and effective for the indications listed on its label before it is approved for marketing. Former FDA Acting Director Steven Galson stated the following about an FDA approval and its associated safety and efficacy:

> What it means when a drug is approved is that the risks are outweighed by the benefits for the indication and under the conditions that are in the label. That just means if the drug is used in the right patients, in the right way, at the right dose, and there aren't drugs that are contraindicated taken with it, that the benefits outweigh the risks. There's a lot that can go wrong that doesn't fit under that definition. But the benefits outweigh the risks for the indication and under the conditions of use that we specify when we approve drugs, and the public should feel very comfortable with the review process. (PBS 2011)

Off-label prescribing is the use of a prescribed medication in a manner different from that approved by the FDA (Stafford 2008). Physicians can legally rely on their professional judgment to use these FDA-approved products in different diseases, different aged patients, or

different doses that are not approved by the FDA. In fact, legal scholars view guiding industry marketing as the primary purpose of FDA labeling. This has led others to conclude that it is not the label but the strength of clinical evidence that physicians should be aware of and use to guide their prescribing (Beck and Azari 1998, Chen et al. 2009). The FDA even condones off-label use when appropriate:

> Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. (FDA 2011)

Others have strongly supported its use, especially in rare diseases for which there are no drugs approved. Given the lack of approved treatments for some diseases, in 1983 the Orphan Drug Act was passed to incentivize research and development that led to FDA approvals for these neglected diseases.

Off-label use can encompass a broad range of prescribing with many different levels of risk. Examples of off-label use are:

- Different disease – an FDA-approved drug to treat blood pressure is used to treat migraine headaches
- Different patients – an FDA-approved drug to treat depression is used in children less than 12 years of age even though it was not studied in this population
- Different dose – an FDA-approved drug to treat a sinus infection is used at a higher dose than listed in the FDA-approved label.

Given the vast differences and risks under the off-label umbrella, some have even suggested a three-level evidentiary categorization system: supported, suppositional, and investigational (Largent 2009).

The US has seen the dangers of off-label use, such as the long-term use of the drug combination "Fen-Phen," the components of which were approved as single agents for short-term use. Recently, the significant off-label use of Avastin® in unapproved cancers at a cost of greater than $50,000 per year has not gone unnoticed by payers, yet its use was welcomed by some in the treatment of macular degeneration with a per treatment cost of < $150 compared to the leading alternative at $2,000 per treatment.

Fairman (2010) discusses the controversy and contradiction based on the actions of the FDA, the Centers for Medicare & Medicaid Services (CMS), and the Department of Justice (DoJ). Although it is legal in the US for physicians to use drugs off-label, it is not legal for drug companies to market FDA-approved drugs for off-label uses. While the FDA is perceived as relaxing regulation, the DoJ is increasing its activities. This legal action against the promotion of prescription drugs for off-label uses has resulted in billions of dollars in settlements and fines (examples: Pfizer's settlement for $2.3 billion in 2009, Eli Lilly's charge for $1.4 billion in 2009, Astra Zeneca's payments of $520 million in 2010, and Allergan's guilty plea resulting in $600 million in payments) (Fairman 2010, Law 2007). Off-label marketing is very different from off-label use, and this study does not address the implications of off-label marketing.

While the medical, regulatory, payer, pharmaceutical, and legal communities readily acknowledge that off-label prescribing is common, it appears that only one study (Lenk et al. 2009) has measured patient perceptions and attitudes toward this prescribing behavior. This study was based on 94 German parents and assessed their awareness and attitudes toward the use

of unlicensed products in their children. Patient advocates for rare disease populations discuss the need for effective and safe therapies that better treat the target disease and therefore include the concept of off-label use in their communications (NORD 2011). But even in these patients, who may be more aware of the concept of off-label use than the broader population, the effect on decision making has not been studied. A void exists in the literature for studies assessing patients' attitudes toward off-label use, perceived value of an FDA-approved indication, and decision making to comply with the physician prescribing of off-label drugs.

Medication Compliance/Adherence

Compliance is defined as the extent to which a patient takes the medication as prescribed by the health care provider. Adherence is also used to describe this behavior, as it suggests the addition of patient agreement with the instructions and addresses the criticism that compliance suggests patient involvement is passive (Osterberg and Blaschke 2005, Bentley et al. 1999).

There are numerous ways to deviate from perfect compliance with prescriber instructions. These actions can be either volitional or nonvolitional. When the patient makes a conscious choice to be noncompliant with the instructions, it is a volitional action. There are also various types of compliance (Table 2-1).

With noncompliance costs estimated at > $250 billion annually (Express Scripts 2010), it is difficult not to feel compelled to address this problem despite its complexity. It also must be addressed with an open mind and research, as intuition may lead many astray. Kocurek (2009, p. 80) discusses the common assumption that difficulty with taking medications occurs primarily in older adults: "[H]owever, age itself has not been identified as a risk factor for medication nonadherence." Jo (2006) found that patients < 65 years of age and with fewer comorbidities

were more likely to be nonadherent. Lobb (2007) identified younger patients as less likely to be compliant initially when out-of-pocket costs were high.

Table 2-1: Definitions of Varying Types of Compliance

Initial noncompliance	The instance whereby patients fail to receive the medication prescribed for them. It includes both unpresented and unclaimed prescriptions.
Partial compliance	The process of taking a prescribed and dispensed medication at a level less than was intended by the prescriber. It includes premature discontinuation of therapy, missed doses, and late refills.
Compliance	The process of taking a prescribed and dispensed medication precisely as intended by the prescriber.
Hypercompliance	The situation in which a patient takes a prescribed and dispensed medication at a level over the prescriber's intended dosing interval.

Source: Bentley et al. 1999

After a review of the literature (1966 to 2002) on compliance among community-dwelling older patients, Vik et al. (2004, p. 303) found that "polypharmacy and poor patient–healthcare provider relationships (including the use of multiple providers) may be major determinants of nonadherence among older persons, with the impact of most sociodemographic factors being negligible. There is little consensus regarding other determinants of nonadherence." The authors also report that as high as 11% of hospitalizations among older patients are attributable to nonadherence (Vik et al. 2004). Improvements in patient-health care provider relationships may lead to a reduction in the burden of noncompliance.

Patient Trust in Physician

Thom et al. described trust:

It's been broken, misplaced, abused, shaken, and violated. Occasionally it's repaired and rebuilt. Trust is a vulnerable and fragile commodity, vaunted in the marketplace,

> acknowledged in every profession, yet perniciously difficult to quantify. Marketers measure its value in brand loyalty, customer retention, product satisfaction, and sales. In the health care marketplace, the absence or presence of trust in patient-provider relations can have life-changing consequences. A person who trusts a provider is more likely to seek care, to comply with treatment recommendations, and to return for follow-up care than a person who has little trust in a specific provider or health care system. Doesn't that alone make it something worth measuring? (Thom et al. 2004, p. 124)

The same researchers (Thom et al. 2004, p. 126) described patient trust as "a collective good, similar to 'social capital,' that is necessary for an effective health care system."

In studies with patients, the following categories of physician behavior with a positive effect on trust generally were found: competency, communication, caring, honesty, and partnering. These are similar to interpersonal trust-promoting factors identified in psychology and sociology research: (1) greater perceived mutual interests, (2) clear communication, (3) a history of fulfilled trust, (4) less perceived difference in power with the person being trusted, (5) acceptance of personal disclosures, and (6) an expectation of a longer-term relationship. "[T]hese associations suggest approaches that would be expected to increase patient trust, such as emphasizing mutual interests (the patient's health); checking patients' understanding of communication; taking opportunities to fulfill trust (phoning with test results); reducing power differences (sharing information); responding to patients' self-disclosures in a supportive and nonjudgmental way; and promoting continuity of care" (Thom et al. 2004, p. 130).

The first scale to measure this important driver of behavior was developed in 1990 (Anderson and Dedrick 1990), and since then several teams have been working in the area (Kao et al. 1998, Hall et al. 2002, Thom et al. 1997, Thom et al. 1999, Safran et al. 1998). The

concept may readily appear multidimensional in a preliminary assessment, and the researchers each essentially identified five overlapping domains/dimensions consisting of fidelity, competence, honesty, confidentiality, and global trust (Greenbridge 2011). However, efforts to identify and separate these unique dimensions have been unsuccessful. Trust appears to be unidimensional. In fact, "the failure to differentiate between competence and other aspects of trust is especially notable" (Hall et al. 2002, p. 313).

Assessment of trust is further complicated by the realization that trust exists in many forms, given the complex relationships between the patient and the health care community, which is made up of individual physicians, the medical profession, other health care professionals and providers, institutions, payers, and more. It is also important to note the distinction "between interpersonal trust, which characterizes a relationship between two individuals, such as a specific doctor-patient relationship, and institutional or system trust, which characterizes attitudes toward collective or social organizations" (Hall et al. 2002, p. 297). The large domain of trust seems to move beyond the individual physician; thus, the development of scales to test trust in these different health care participants (e.g., payers or insurance companies) is also important.

It is interesting to note that trust varies by religion (Benjamins 2006) and race (Keating 2004). Despite the complexity of trust and finding that trust formed with an individual physician is correlated with higher continuity (Mainous 2001), high levels of trust with specialists were found after only a single visit (Keating et al. 2004).

Lake et al. (1999-2000) demonstrated that HMO enrollees had a lower likelihood of expressing trust in their physicians than non-HMO patients. Given the complex structure of payers and the various financial relationships with physicians, one could be concerned about the

impact on trust in physicians. To study this, members of two similar HMO plans were randomized to intervention and control groups. The experimental arm was informed "how the HMO paid their primary care physician. Separate disclosures were developed for each plan, one describing primarily capitation payment, and the other (mixed-incentive plan) describing fee-for-service payment with a bonus that rewards cost savings, satisfaction, and preventive services" (Hall et al. 2002, p. 197). The disclosures, albeit they communicated more of the positive than the negative features of these incentives, had in informative aspect that may be similar to disclosing the existence of off-label prescribing to patients. The researchers' disclosure:

> [D]oubled the number of subjects with substantial knowledge of the physician incentives and halved the number with no knowledge. Nevertheless, the disclosures had no negative effects on patient trust of either physicians or insurers. The capitated plan disclosure had a small positive effect on trust of physicians. Disclosing the positive and negative features of incentives and increasing knowledge of these incentives does not, in the short term, reduce trust in physicians or insurers and may have a mild positive impact on physician trust, perhaps as a consequence of displaying candor and increasing understanding of positive features. (Hall et al. 2002, p. 197)

In 2002, Thom et al. (p. 476) found that "[p]atients with a lower level of trust in their physician are more likely to report that requested or needed services are not provided" and then suggested that "[u]nderstanding this relationship may lead to better ways of responding to patient requests that preserve or enhance patient trust, leading to better outcomes." Additionally, trust in the medical profession has been found to be a significant predictor of many self-reported patient behaviors, including following physician treatment recommendations and willingness to rely on physician judgment (Trachtenberg et al. 2005, Thom et al. 1999).

Trust in the physician also affects initial compliance via willingness to pay. Lower levels of trust in physicians were associated with an increased likelihood of forgoing medication with higher out-of-pocket costs. Only in the context of low levels of trust in physicians did the researchers find an association with low income and cost-related adherence. Researchers concluded that a "trusting physician relationship may moderate the impact of cost pressures on patients' medication adherence. More generally, addressing noncost barriers to adherence may reduce rates of cost-related medication underuse" (Piette et al. 2005, p. 1749).

Appropriately identifying the antecedents and determinants of trust will enable better interventions in this important and complex relationship. The importance of understating the connection between trust and compliance grows as physicians move from a paternalistic role to more collaborative care involving the patient in health care decisions (Hammond and Lambert 1994) and as the influence from third parties grows. This change has even caused some to suggest that "too much trust" might harm patients in paternalistic relationships and as managed care grows (Gatter 2004, Buchanan 2000, Davies and Rundall 2000).

Patient Involvement in Medical Decision Making

In their review of the literature, Say and colleagues (2005, p. 102) found that patients' preferences of involvement in medical decision making are influenced by "demographic variables (with younger, better educated patients and women being quite consistently found to prefer a more active role in decision making), their experience of illness and medical care, their diagnosis and health status, the type of decision they need to make, the amount of knowledge they have acquired about their condition, their attitude towards involvement, and the interactions and relationships they experience with health professionals. Their preferences are likely to develop over time as they gain experience and may change at different stages of their illness."

Interestingly, across multiple diseases, approximately two thirds of patients expressed a desire for shared decision making with the physician (Trachtenberg et al. 2005, Arora et al. 2000), even in cancer (Bruera et al. 2001). Patients' desire to be involved in decision making and the treatment process was inversely proportional to patients' disease criticality in numerous diseases (Levinson et al. 2005, Arora et al. 2000).

The connection with trust and involvement in medical decision making is not necessarily intuitive. Trachtenberg and colleagues (2005, p. 345) describe the challenging relationship:

> Both patient trust and active patient involvement are desirable in their own right and because they are associated with improved health outcomes. Paradoxically, however, it might be thought that these 2 attributes are in sharp conflict.
>
> Patient trust might be more consistent with a deferential style of patient-physician interaction in which patients are passive, in contrast to assertive patient questioning or limitation of physician authority which might be indicative of patient distrust. If so, then pursuing active patient involvement might lead to lower trust, or promoting trust might lead to more passive patients, either of which might compromise optimal treatment relationships and health outcomes. At a minimum, it is a conceptual puzzle how these 2 views of desirable attributes of medical relationships can coexist without each taking account of the other view.

In their study of American adult patients (n = 553) who have seen a physician or other health professional at least twice in the past two years, they assessed preference of the patient's role in medical decision making, trust in physician, trust in medical profession, and satisfaction with care. They found that the most significant predictor of patients' preferred role in medical decision making was trust in the medical profession (not the specific physician). Views also

varied by sex, age, health, education, income, number of visits/years with physician, past dispute with a physician, and satisfaction with care. Views varied slightly by trust in the specific physician.

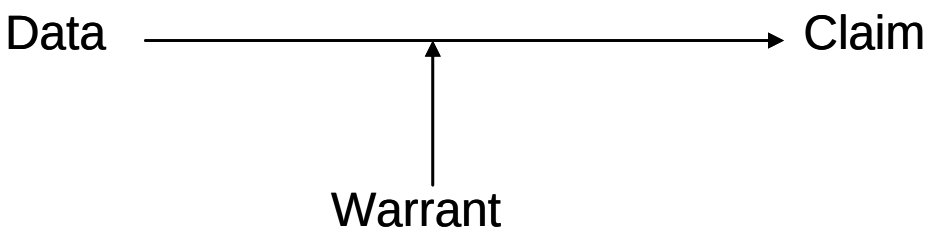
Patient Decision Making

It is probably difficult to overestimate the complexity of patient decision making. Fincham and Wertheimer (1985) identified more than 250 social, economic, medical, and behavioral factors associated with noncompliance.

In decision making, beliefs determine intentions which determine actual behavior (Ajzen and Fishbein 1980). The theory of planned behavior has been studied extensively in many settings; however, it failed to explain how beliefs were formed.

Beliefs are expectations about reality that are formed by practical reasoning or arguments (Smith et al. 1991). Smith, Benson, and Curley's model of belief formation was influenced by the work in argument theory of Toulmin (1958). In Toulmin's model, data are assessed to form claims through a process of judgments and reasoning (Figure 2-1).

Figure 2-1: Toulmin's Argument Model



Source: Toulmin 1958

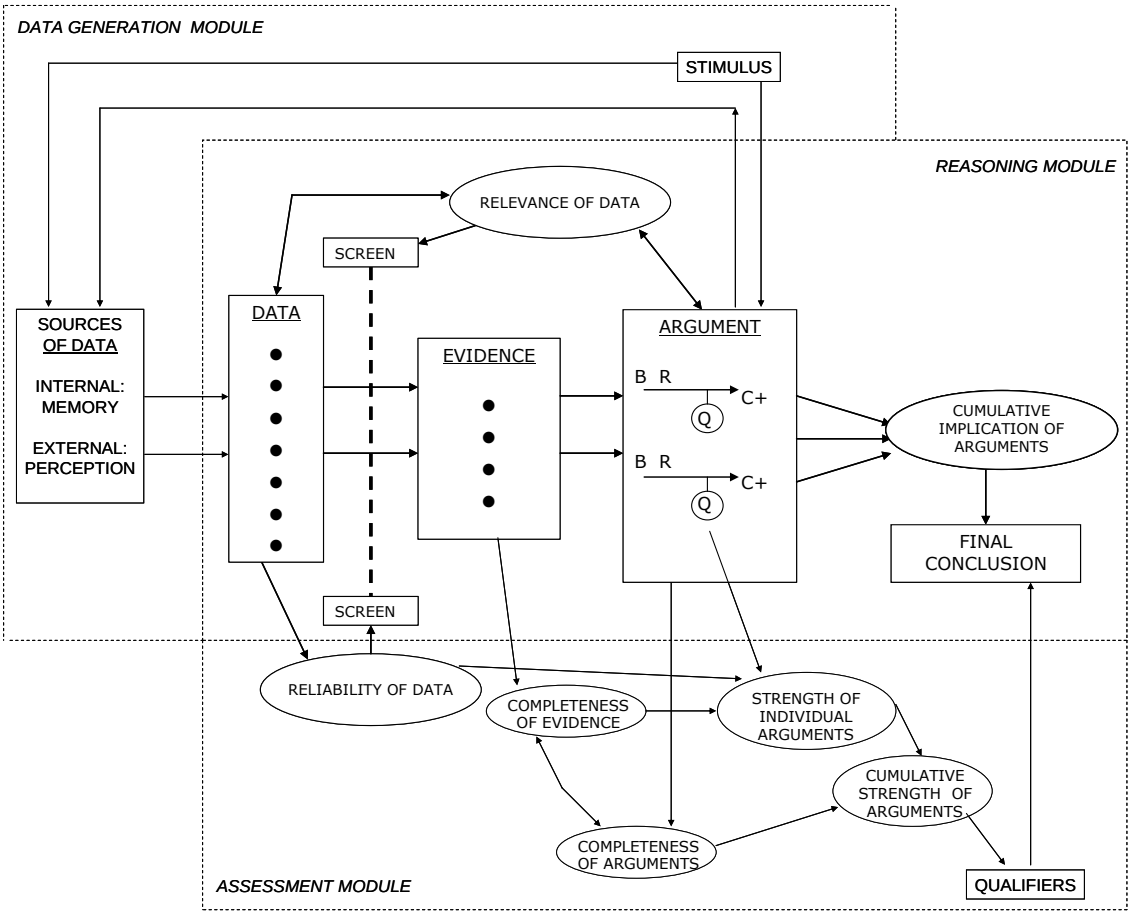
An argument or claim is determined by acquisition of the data and the warrant or judgment made about the data. The warrant provides structure to an argument and justifies the leap from data to

claims (Boller et al. 1993). Warrants are the key elements that reflect the assumptions of an argument (Smith et al. 1991) and drive the categorization of arguments into three main types:

1. Substantive arguments − The warrant in substantive arguments is an assumption concerning the relationship existing among phenomena in the external world. This includes causal arguments (e.g., my positive experience with a drug shows the drug is of value to me).
2. Authoritative arguments − Unlike substantive arguments, authoritative arguments consist of factual reports or statements of opinion. The warrant in an authoritative argument affirms the reliability and credibility of the source (e.g., the drug is of value to me because the knowledgeable physician said it would be beneficial to me).
3. Motivational arguments − In motivational arguments, the data consist of one or more statements that may have been established as claims in a previous argument or series of arguments. The warrant indicates a motive for accepting the claim by linking it with inner drive, desire, value, emotion, aspiration, or a combination of such forces.

Although the work of Smith, Benson, and Curley is based on this Theory of Argument (Toulmin 1958), it substantially varies in two areas: (1) they propose three modules (Figure 2-2) that work interactively, not sequentially, and (2) they introduced screens of relevance and reliability (Figure 2-3) through which information is judged. In the first module, data are retrieved internally from memory or externally through perception. In the second module, these data are judged against the concepts of relevance and reliability to determine whether the data are worthy and applicable for argument construction. Finally, in the third module, referred to as the reasoning or argument construction, these data are transformed into beliefs.

Figure 2-2: Smith, Benson, and Curley Model of Belief Processing



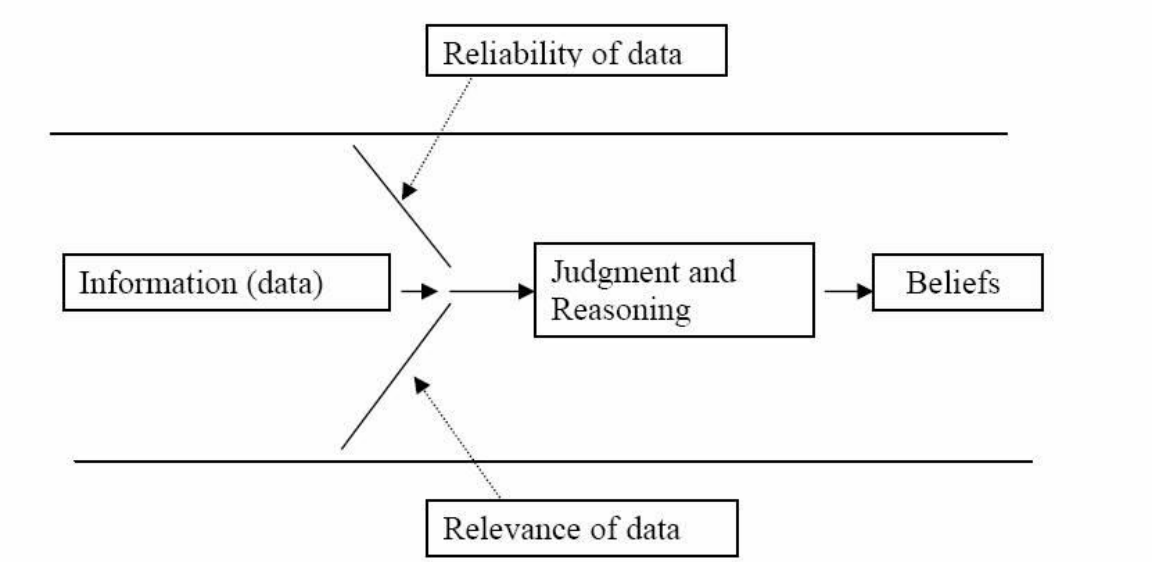
Source: Smith et al. 1991

Experiences have been shown to play a mixed role in the arguments that are used to form beliefs. West et al. (2003, p. 1140) examined the role of experience in the formation of patients' beliefs about pharmacist trustworthiness and found that as patients "gain experience with a situation, they are more likely to use their experience to form causal arguments and less likely to rely solely on external sources [to form beliefs]." However, a study by Jalnawala and Wilkin (2004) found that authoritative arguments induced more favorable beliefs about the advertised medication than causal arguments.

Relevance and Reliability Measures

A depiction of this portion of the reasoning module (Jalnawala 2005) is presented in Figure 2-3.

Figure 2-3: Information to Belief, the Role of Relevance and Reliability



Source: Jalnawala 2005

Here the data that are considered to be relevant and reliable are admitted through the cognitive screen, while the data that are considered irrelevant and unreliable are discounted, thereby exerting minimal influence on beliefs.

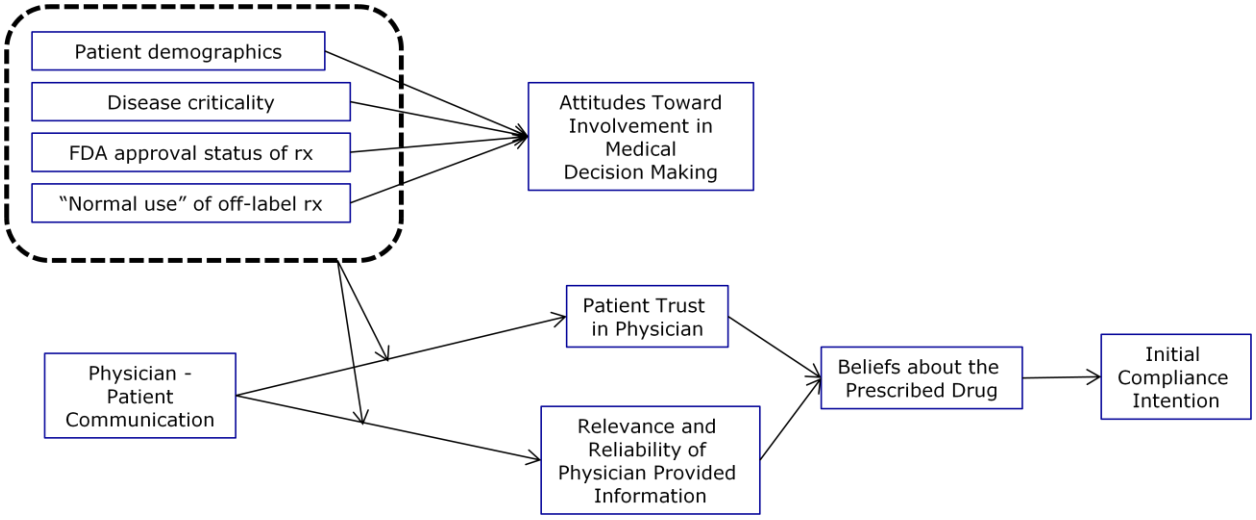
The role of relevance and reliability judgments in belief formation has been addressed in several studies (Sewak 2002, West et al. 2004, Jalnawala and Wilkin 2004, Lobb 2007, King and Wilkin 2004). Patients have used relevance judgments to assess the utility of the information and reliability judgments to assess the dependability of pharmacists (West et al. 2004). In a consumer study of weight loss supplements, the relevance and reliability of the information were more predictive of beliefs than source credibility (King and Wilkin 2004). The judgments of

relevance and reliability seem to be more powerful regulators of information in the process of belief formation than the judgment of a source's credibility (Jalnawala 2005).

Conceptual Framework

The model shown in Figure 2-4 was developed to show the proposed relationships among the studied concepts.

Figure 2-4: Conceptual Framework



Research Questions

The literature review revealed that:

(a) Widespread off-label use of pharmaceuticals exists and level varies by disease state.

(b) Little is known of patients' attitudes and perceptions of off-label use.

(c) Compliance can be positively correlated with disease severity/criticality.

(d) Trust in physicians has increased compliance with treatments.

(e) Patient involvement in medical decision making has been shown to decrease with disease severity/criticality.

(f) Physician-provided communications have been demonstrated to reduce the level of volitional noncompliance.

(g) The patient-judged relevance and reliability of the information provided by the health care provider can determine the beliefs about the drug and intentions to be compliant.

These givens led to several research questions:

- What are the roles of disease criticality, FDA approval status of the prescribed drug, and the "normal" level of off-label use in beliefs formed about the prescribed drug, level of trust in physicians, level of involvement in medical decision making, and intentions of initial compliance?
- What are the roles of relevance and reliability judgments of the physician-provided information in the beliefs formed about a prescribed drug and the intentions of initial compliance?
- How do the roles of these elements differ in a population of elderly patients when compared to younger patients?

CHAPTER III

RESEARCH DESIGN AND METHODS

This chapter discusses the study design, sampling, operationalization of the variables, questionnaire design, data collection, and data analysis plan. The method was approved by the University of Mississippi Institutional Review Board.

Study Design

The goal of this study was to examine the effects of off-label use on patients' trust of the physician, involvement in medical decision making, initial compliance, and beliefs toward the drug. A cross-sectional design, the most commonly used survey design (Singleton and Straits 1999), was used in this study. Data were collected using a self-administered online questionnaire which asked respondents about their opinions on various factors under different off-label scenarios (presented in the Appendix) based on a $2 \times 2 \times 2$ design. Each respondent was exposed to one of eight scenarios with the following manipulations: (1) disease (varying by criticality), (2) the normal level of off-label use for this disease, and (3) the FDA approval status of the prescription for this disease.

Sampling

Data to test the propositions and hypotheses were collected from a stratified random sample of consumers from an on-line panel. Stratifying by variables correlated with the dependent variables increases the precision of estimates because it systematically introduces

relevant sources of variability in the population into the sample. The strata were based on age, ≥ 65 years of age and < 65 years of age. Those ≥ 65 years of age qualify for prescription drug coverage by Medicare Part D. Previous research has shown differences in initial compliance by age (Lobb 2007). Similar to previous research (Lobb 2007), a quota sampling technique was used to achieve 800 respondents, enabling cell sizes of 50 in the 2 × 2 × 2 design for the ≥ 65 years of age and < 65 years of age arms of the study. The sample was limited to respondents who were current users of prescription drugs and/or who had purchased at least 1 prescription drug in the previous 12 months.

A common criticism of online sample frames is that the sub-population may not reflect the broader population, but this is changing as more US citizens are online (Sheehan 2006). The consumer panels of Research Now, a professional market research company, served as the sample frame, and the demographics of the sample frame can be compared to the US population.

Nonresponse bias was assessed in two manners. First, demographic data were requested from those who did not meet inclusion criteria. Second, the demographics of the sample were tested against the demographics of the full panel, or sample frame.

Operationalization of Dependent Variables

Trust in the Physician

Although scales date back to 1990 (Anderson et al.), the Wake Forest Physician Trust Scale developed by Hall et al. in 2002 is likely the most accepted scale (Thom et al. 2004). A short version of this five-item scale has been validated (Dugan et al. 2004) and even used in a study associated with patient involvement in medical decision making (Trachtenberg et al. 2005). The scale is designed for measuring trust in an individual physician, not trust in the medical profession. This matches the scenario in which the respondent will be asked to assess trust in the

specialty physician prescribing the on-label or off-label drugs. Research has found that even high levels of trust can form in a specialist physician in an initial visit (Keating et al. 2004). Below are the five items that have been modified to assess trust in the scenario's prescribing physician:

After reading each statement, rate how much you agree or disagree with each statement:

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
○	○	○	○	○

1. Sometimes this [oncologist/allergist] cares more about what is convenient for (him/her) than about your medical needs.
2. This [oncologist/allergist] is extremely thorough and careful.
3. You completely trust the [oncologist/allergist]'s decisions about which medical treatments are best for you.
4. This [oncologist/allergist] is totally honest in telling you about all of the different treatment options available for your condition.
5. All in all, you have complete trust in this [oncologist/allergist].

Relevance and Reliability of Information

Supported by the several studies (Sewak 2000, West et al. 20004, Lobb 2007, Jalnawala 2005) and based on the model proposed by Smith et al. (2005), the relevance and reliability of information presented in the scenarios acts as a filter that determines which information becomes evidence for the argument. In previous studies, an eight-item, nine-point semantic differential scale has been used for relevance and reliability assessments (five items for relevance and three for reliability). Given the mixed results of previous studies, an exploratory factor analysis was conducted to assess the dimensionality of the scale to determine whether the two measures were the same or separate constructs. The reliability of the scale was evaluated using Cronbach's alpha.

In this scenario, I believe the information provided by the [oncologist/allergist] is:

Undependable	1	2	3	4	5	6	7	8	9	Dependable
Not helpful	1	2	3	4	5	6	7	8	9	Helpful
Unimportant	1	2	3	4	5	6	7	8	9	Important
Consistent	1	2	3	4	5	6	7	8	9	Inconsistent
Meaningful	1	2	3	4	5	6	7	8	9	Meaningless
Irrelevant	1	2	3	4	5	6	7	8	9	Relevant
Unreliable	1	2	3	4	5	6	7	8	9	Reliable
Useless	1	2	3	4	5	6	7	8	9	Useful

Patient Involvement in Medical Decision Making

The desire of patients to be involved in the decision making of their medical care varies significantly (Arora et al. 2000, Levinson et al. 2005). Approximately two thirds of patients express a desire for shared decision making with the physician (Trachtenberg et al. 2005, Arora et al. 2000), even in cancer (Bruera et al. 2001). The scale below was adapted from the one used by Trachtenberg et al. (2005) to assess the correlation between patients' trust and their attitudes toward seeking care, participating in medical decision making, and adhering to treatment recommendations:

> After reading each statement, rate how much you agree or disagree with each statement regarding the scenario you just read.
>
> Strongly Agree Agree Neutral Disagree Strongly Disagree
>
> 1. I will always follow this [oncologist/allergist]'s recommendations about treatment.
> 2. It is better to rely on the expert judgment of this [oncologist/allergist] than to rely on common sense in taking care of my own body.
> 3. It is better to seek professional help than to try to treat myself.
> 4. Concerning my medical care, I should take complete control.
> 5. Concerning my medical care, the [oncologist/allergist] should take complete control.
> 6. In my future visits with the [oncologist/allergist], I believe I will make all of the final decisions.
> 7. In my future visits with [oncologist/allergist], I believe the [oncologist/allergist] should take the initiative and decide what is best for me.

Belief Measures about the Drug

Previous research has shown that patients will develop different beliefs about the drugs based on different stimuli (Sewak 2000, West et al. 20004, Lobb 2007). These beliefs about a prescription drug were directly measured with eight semantic differential questions Sewak (2000) adapted from the work of Petty and Cacioppo:

I believe that the drug I have been prescribed is:

Bad	1	2	3	4	5	6	7	Good
Unfavorable	1	2	3	4	5	6	7	Favorable
Harmful	1	2	3	4	5	6	7	Beneficial
Useless	1	2	3	4	5	6	7	Useful
Ineffective	1	2	3	4	5	6	7	Effective
Unnecessary	1	2	3	4	5	6	7	Necessary
Dangerous	1	2	3	4	5	6	7	Safe
Not helpful	1	2	3	4	5	6	7	Helpful

The Cronbach's alpha for the belief items in the Sewak study was 0.84. Lobb added three items to measure beliefs about the out-of-pocket prescription costs. The Cronbach's alpha for the three items was 0.69. The items were added to this study as well to assess beliefs about the drug.

Not valuable	1	2	3	4	5	6	7	Valuable
Expensive	1	2	3	4	5	6	7	Cheap
Not worth the cost	1	2	3	4	5	6	7	Worth the cost

The reliability of these scales was evaluated using Cronbach's alpha, and the additional items were evaluated before adding them to the drug belief scale.

Initial Compliance Intention

In previous research, the four-item, nine-point semantic differential scale below has been used to measure intention of patients to request or fill a prescription medication after seeing a

stimulus (West et al., 2004, Jalnawala and Wilkin 2004, Lobb 2007). The scale has been found to be a sufficiently reliable measure of the construct of behavioral intention (Cronbach's alpha = 0.98 in Lobb 2007). The same scale was adapted in the context of physicians' "likelihood to prescribe" a medication and had a Cronbach's alpha = 0.94 (Jalnawala 2005). Compliance after the initial fill was not measured, as that may be driven more by experience with the drug than the information provided by the physician. West et al. (2003, p. 1140) found that the "role of external sources in influencing the formation of beliefs about trustworthiness of a pharmacist may be limited as a patient gains pharmacy experience, as experience is based on causal associations."

Based on the information available in this scenario, how likely are you to purchase this prescribed drug?

No chance	1	2	3	4	5	6	7	8	9	Sure to purchase
Likely	1	2	3	4	5	6	7	8	9	Unlikely
Not possible	1	2	3	4	5	6	7	8	9	Very possible
Certain not to purchase	1	2	3	4	5	6	7	8	9	Certain to purchase

Operationalization of Independent Variables

The three variables that set up the 2 × 2 × 2 design and the resulting 8 scenarios to be seen by the respondent were (1) disease state, (2) a disease state specific measure of "normal" off-label use, and (3) the FDA approval status of the drug for the specific disease.

Disease Criticality

The amount of off-label use varies by disease state (Radley 2006) and can skew high for oncology and allergies (Radley 2006, Peppercorn 2008, Poole 2004, Soares 2005). Depending on the disease, prescribers and patients have historically been willing to accept different risks with regard to drug use (e.g., a drug that significantly reduces immune levels may be used to

treat cancer but would not be used to treat a common ear infection) (Harrison et al. 2005, Denig et al. 1988). Patient compliance has also been found to vary by disease state and perceptions of the associated risks (Christensen 1978, Porter 1969). Cancer and allergies were selected for this study to represent actual disease areas with high levels of off-label use and to represent differences between critical, life-threatening diseases and common, non-life-threatening ailments. The variable was coded so that a value of "0" was for allergies and "1" was for cancer.

"Normal" Off-Label Use

To convey to the patient that the physician is or is not acting in accordance with medical norms, two levels of "normal" off-label use were selected. To convey a high or common use of off-label prescribing in the specific disease, the patient was told that a "national survey shows 75% of the patients in the US with this type of [cancer/allergy] receive drugs that are approved by the FDA to treat this type of [cancer/allergies]. The other 25% receive drugs that are not approved by the FDA to treat this type of [cancer/allergies]." To convey a minority use of off-label prescribing, the percentages were reversed. The 75% metric is representative of the higher levels found in studied diseases and has been associated with oncology and psychiatry (Radley et al. 2006 and Soares 2005). The variable was coded as having a value of "0" for 25% use of off-label drugs and "1" for 75% use of off-label drugs.

FDA Approval Status of the Drug for the Specific Disease

Consumers have shown a high level of confidence in the safety and effectiveness of drugs approved for use in the United States (PWC 2010). However, no studies have assessed patients' opinions or assumptions of FDA approval for their uses of the product. Patients may assume their FDA-approved drugs are approved for their specific use. The respondents in this study

were explicitly told that the prescription they received was written for a drug that a) was approved or b) was not approved by the FDA for this type of [cancer/allergies]. The variable was coded as having a value of "0" for FDA approval and "1" for non-FDA approval.

Other Independent Variables

Trust in the FDA

Previous research has shown that despite 93% of patients being confident about the safety and effectiveness of drugs approved for use in the United States, roughly one third to over one half feel negatively about how the FDA is doing its perceived job (Pricewaterhouse Coopers 2010, Harris Interactive 2008). These studies measured expectations and perceptions but did not appear to inform the respondents of the stated responsibilities of the FDA. In informing all respondents of the responsibilities of the FDA with regard to drugs especially, the following information from the FDA (2011) Web site was provided:

> FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
>
> FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

To measure trust in the FDA, the five-item scale that was used to measure trust in physicians by Dugan et al. (2004) was adapted. A five-point Likert-like scale with the items shown below was used to measure trust in the FDA. The sixth item was added to assess trust in the FDA specifically with regard to regulating prescription drugs.

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. The FDA is extremely thorough and careful.
2. I completely trust the FDA's decisions about which medical treatments are safe and effective.
3. The FDA would never mislead me about anything.
4. Sometimes the FDA cares more about what is convenient for them than about the patients' medical needs.
5. All in all, I trust the FDA completely.
6. All in all, I trust completely in the FDA's ability to regulate prescription drugs.

Opinions of Off-Label Use

At this time, no studies have assessed patients' perspectives of off-label prescribing. The following description of off-label use was given:

> This study will involve off-label prescribing — the prescription of a medication in a manner different from that approved by the FDA. In the United States, since 1962, in order for prescription drugs to be allowed in the market, they must have been proven safe and effective when treating the disease states that are listed in each drug's label, or **on label**. One previous FDA leader simplified the meaning of an FDA approval by saying something similar to this: FDA approval means if the drug is used in the right patients, in the right way, at the right dose, then the benefits outweigh the risks.
>
> However, once approved by the FDA and marketed in the United States, doctors can legally rely on their professional judgment to use these FDA approved products to treat different diseases, even if those uses are not specifically approved by the FDA. This is called **off-label** use.

To explore the beliefs of patients about this phenomenon, the following items were created and agreement was tested:

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
○	○	○	○	○

1. I believe the majority of prescriptions in the US are prescribed on label to treat diseases for which they are FDA approved.
2. I believe it is safe to use FDA approved drugs off label to treat other diseases than for what they were originally approved.
3. I believe most physicians know when a drug is FDA approved or not approved to treat the disease in which they are prescribing it.
4. I believe insurance companies check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.
5. I believe pharmacists check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.
6. I believe all of the drugs I take are on label - FDA approved for the disease in which I use the drugs.
7. I believe drugs that are used on label - FDA approved for a disease - are always more effective than drugs that are used off label – not FDA approved for that disease.
8. I believe drugs that are on label - FDA approved for a disease - are always safer than drugs that are off label - not FDA approved for that disease.
9. I only want to be prescribed drugs that are on label - FDA approved to treat the specific disease I have.
10. I believe doctors who prescribe drugs off label for diseases for which the drugs are not FDA approved are superior doctors.
11. I believe doctors who prescribe drugs off label - for diseases for which the drugs are not FDA approved - only do so because it is the best option for their patient.
12. I believe doctors only prescribe drugs off label - for diseases for which the drugs are not FDA approved - for very rare diseases, not for more common ones.
13. For children, I believe doctors only prescribe drugs on label - for diseases for which the drugs are FDA approved.

Demographic Variables

To reduce respondent fatigue, demographic assessments were placed at the end of the questionnaire. The demographic variables included age, gender, ethnicity, education, marital status, annual household income, religion, and employment status. Lobb (2007) found that patients > 65 years of age were higher in initial compliance intent than younger patients.

Social Desirability Assessment

Previous studies have shown positive correlation and no correlation between social desirability and compliance measures (Wang et al. 2002, Burge et al. 2005). Of the several techniques used to control social desirability response (Paulhus 1991), the demand reduction and covariate techniques were selected for use. Demand reduction technique is based on assuring respondents of their anonymity. The covariate technique involved administering the short version of the Marlowe-Crowne Social Desirability Scale developed by Strahan and Gerbasi (1972) along with the content measures. This short form, based on a scale using 1 = Strongly disagree to 7 = Strongly agree, has been found to be superior to other forms (Fischer and Fick, 1993):

1. I always try to practice what I preach.
2. There have been occasions when I took advantage of someone.
3. I have never been irked when people expressed ideas very different from my own.
4. At times I have really insisted on having things my own way.
5. I am always willing to admit it when I make a mistake.
6. I like to gossip at times.
7. I never resent being asked to return a favor.
8. I sometimes try to get even rather than forgive and forget.
9. I have never deliberately said something that hurt someone's feelings.
10. There have been occasions when I felt like smashing things.

Correlations were run between the social desirability measure and all other measures.

Questionnaire Design and Pretesting

The self-administered online questionnaire followed the order described here. After reviewing and responding to information about the role of the FDA and an explanation of off-label use, the respondents were given one of eight scenarios. They were asked to imagine themselves in a situation in which they were sick. To remove bias associated with their current trust in the patients' primary care physicians, the scenarios had them first seeking care, as one commonly would, from their primary care physician who then sends them to the appropriate specialist based on the illness. To impose risk with the drug that may not exist with a short course of therapy, the patients were told they would have to take it daily for six months. After reviewing the scenario, the respondents were given the assessments for (1) trust in physician, (2) the relevance and reliability of the information provided by the physician, and (3) patient involvement in medical decision making. Next, the respondents were told that they take the prescription of the specialist to the pharmacy to be filled and the copayment is similar to other prescriptions they have received in the past. Beliefs about the prescribed drug and initial compliance were then measured. Social desirability and demographics were assessed, and the survey ended with a respondent debrief. A copy of the questionnaire is shown in the Appendix.

To assess for face and content validity, the questionnaire was pretested with a convenience sample comprised of Medicare Part D patients (n=3) and commercial patients < 65 years of age (n=4). Following testing, these respondents were debriefed. The same screening criteria were used as in the main study. Manipulation checks were based on differences derived from the manipulations with the disease state and levels of off-label use of drugs for that disease. The manipulations were determined to have the desired perception.

Data Collection and Cleaning

After approval was obtained from the University of Mississippi's Institutional Review Board, the survey was pre-tested as described. For the main data collection a professional market research company, Research Now, was contracted to administer the survey to its online consumer panel that met the screening criteria.

Using the on-line method of collection, the responses were entered directly into an electronic database. Although the likelihood of data entry errors was low using this method, the data were still checked for outliers and errors.

Microsoft® Excel (version 2007) and SPSS® (version 19) were used to manage and analyze the data.

Analysis Plan

An analysis plan was developed to assess the research propositions and hypotheses. Given the general lack of studies assessing patients' attitudes and perceptions of off-label use, propositions were used in lieu of hypotheses. When theoretical support existed, the hypotheses were tested.

All tests of significance were conducted at the 0.05 level of significance. Demographic variables and other descriptive statistics were used to characterize the respondents. For measures of beliefs about the medication, likelihood to purchase the medication, relevance and reliability of the information presented by the specialists, and patient involvement in medical decision making, the scale scores were summed. Cronbach's alpha was used to measure reliability of the scales. Values greater than 0.7 were considered reliable (Hair et al. 1998). Summated scales have been found to reduce measurement error by using multiple indicators to reduce the reliance

on a single response and maintain parsimony by representing multiple aspects of a concept in a single measure (Hair et al. 1998).

After assessing the scale's internal consistency using Cronbach's alpha, each scale's items were examined using exploratory factor analysis (EFA). The exploratory factor analysis was used to assess the factor structure of the data (Hair et al. 1998).

Research Question 1. What are the roles of disease criticality, FDA approval status of the prescribed drug, and the "normal" level of off-label use in beliefs formed about the prescribed drug, level of trust in physician, level of involvement in medical decision making, and intentions of initial compliance?

The analysis of the research propositions tested each of the directional propositions in its null form. For the following propositions, *t* tests were used to determine whether the two group means were statistically different from each other (Hair et al. 1998).

P_1 The prescribing of an FDA-approved drug leads to a greater likelihood of patient initial compliance intention with a prescription than prescribing off-label.

P_2 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to a lower likelihood of patient initial compliance with a prescription than prescribing an FDA-approved drug.

P_3 The prescribing of an off-label FDA-approved drug in a more critical disease leads to a greater likelihood of patient initial compliance with a prescription than in a less critical disease.

P_4 The prescribing of an FDA-approved drug leads to a greater trust in the physician than prescribing off-label.

P_5 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to lower trust in the physician than prescribing an FDA-approved drug.

P_6 The prescribing of an off-label FDA-approved drug in a less critical disease leads to a lower trust in the physician than in a more critical disease.

P_7 There is no difference in the likelihood of patient involvement in medical decision making when an FDA-approved drug is prescribed than when an off-label drug is prescribed.

P_8 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an FDA-approved drug when the norm is to use FDA-approved products than prescribing an off-label drug.

P_9 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an off-label drug in a critical disease than in a less critical disease.

P_{10} The prescribing of an FDA-approved drug leads to stronger positive beliefs about the drug than prescribing off-label.

P_{11} The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to weaker positive beliefs about the drug than prescribing an FDA-approved drug.

P_{12} The prescribing of an off-label FDA-approved drug in a less critical disease leads to weaker positive beliefs about the drug than in a more critical disease.

Exploratory multiple regressions were used to measure the effects of diseases state (DISCRIT), normal level of FDA-approved product use (OFFUSELVL), and FDA approval

status (FDASTAT) on beliefs of the drug initial compliance intent, trust in the physician, and involvement in medical decision making:

Beliefs of the drug = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

Initial compliance = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

Trust in the physician = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

Involvement in medical decision making = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

Multiple regression allows for the simultaneous assessment of relationships between each independent variable and the dependent measure (Hair et al. 1998). Multiple regression was selected for its ability to model interactions, including two-way and three-way interactions, and identify issues such as multicollinearity. The variables including interactions were all entered in one step, and the interactions were removed as they were found not to be significant. The data were assessed to ensure that they met the assumptions of regression, namely linearity of the phenomenon, constant variance of the error terms, independence of the error terms, and normality of the error terms (Hair et al. 1998).

Research Question 2. What are the roles of relevance and reliability judgments of the physician-provided information in the beliefs formed about a prescribed drug and the intentions of initial compliance?

H_1 The higher the judged relevance and reliability of the physician-provided information are, the stronger the positive beliefs formed about the prescription product will be.

H_2 The higher the judged relevance and reliability of the physician-provided information are, the greater the initial compliance intention will be.

For hypotheses 1 and 2, a bivariate correlational analysis was run. Pearson's correlation coefficient was used as the measure of association between the physician-provided information relevance and reliability and (1) beliefs about the medication and (2) initial compliance intention.

Research Question 3. How do the roles of these elements differ in a population of elderly patients when compared to younger patients?

These propositions for the age-related differences were tested using a series of independent *t* tests:

P_{13} Elderly ($\geq$ 65 years old) patients differ from younger patients in responses to behavior of off-label use, trust in physician, and initial compliance intentions.

P_{13oA} In the same off-label scenarios, elderly patients do not differ from younger patients in the strength of the beliefs formed about the prescription.

P_{13oB} In the same off-label scenarios, elderly patients do not differ from younger patients in their initial compliance intentions measured by a multi-item scale.

P_{13oC} In the same off-label scenarios, elderly patients do not differ from younger patients in their judgments of relevance and reliability of physician-provided information.

P_{13oD} In the same off-label scenarios, elderly patients do not differ from younger patients in their trust in physicians.

P_{13oE} In the same off-label scenarios, elderly patients do not differ from younger patients in their involvement in medical decision making.

CHAPTER IV

RESULTS

Despite the use of off-label prescribing being common, no studies have investigated the effect of non-FDA approved uses of pharmaceuticals on patient decision making. This study was conducted with Research Now's online panel with the goal of obtaining 800 responses between 2 age groups: (1) elderly (≥ 65) and (2) nonelderly (< 65). The results of this study designed to enhance understanding of the effects of off-label prescribing are presented here.

Data Cleaning and Manipulation

Data were checked for outliers and errors. Of the 838 respondents, 8 individuals initially responded to the age-related questions used to select scenarios in a manner that later did not appropriately match their stated year of birth. These were eliminated from the sample.

All fields were required for completion of the survey; thus, no missing data were handled. Reverse-coded items were recoded for appropriate scale assessments and summations.

Demographics

The sample frame was an online panel. The average age for respondents was 59.0 years, with 60% being female. The panel was educated, with almost 70% completing at least a 2-year degree program, and 87.6% reported being white/Caucasian. Household income was reported as more than $45,000 for 76.4% of respondents. The demographic data are shown in the aggregate

and for the elderly and nonelderly groups in Tables 4-1 and 4-2. Group means are reported in Table 4-3.

Non-Response Bias

T-tests and chi-square tests were conducted to determine if differences in demographic variables and dependent variables existed between the first 10% of respondents and the last 10% of respondents. These tests failed to identify significant differences between early and late responders. Summary of these analyses can be found in Tables 4-4 thru 4-9.

Scale Reliability and Factor Analysis

The study consisted of seven scales. The Cronbach's alpha, depicted in Table 4-10, was used to measure reliability of the scales. Values greater than 0.7 were considered reliable (Hair et al. 1998). Social desirability was the only scale below the 0.7 threshold.

In a previous study (Lobb 2007) the three items shown below were added to the drug belief scale. The three-item scale alone had an alpha of 0.692 in the previous study.

Not valuable	1	2	3	4	5	6	7	Valuable
Expensive	1	2	3	4	5	6	7	Cheap
Not worth the cost	1	2	3	4	5	6	7	Worth the cost

However, in this study the three-item scale had an alpha of .241 in the oncology scenarios and .272 in the allergy scenarios. When added to the previously studied drug belief scale (Sewak 2000, West et al. 20004, Lobb 2007), the alpha for the oncology scenarios was reduced from 0.923 to 0.897 and the alpha for the allergy scenarios was lowered from 0.931 to 0.912. These items were not used as part of the drug belief scale.

Table 4-1: Sample Description (1of 2)

	Group %		
	Nonelderly	**Elderly**	**Total**
	n = 409	*n* = 421	*n* = 830
Gender			
Male	29	52	40.0
Female	71	48	60.0
Age			
18 – 24 years	3.1		2.3
25 – 34 years	16.4		8.4
35 – 44 years	18.1		8.9
45 – 54 years	26.1		14.5
55 – 64 years	36.3		16.6
65 years or older	0	100	49.3
Marital Status			
Single, never married	19.7	2.9	11.4
Unmarried couple living together	6.9	2.0	4.5
Married	59.6	71.4	65.4
Separated	0.7	0.2	0.5
Divorced	10.5	13.2	11.8
Widowed	2.1	10.3	6.1
Decline to answer	0.5	-	0.3
Race			
Black/African American	5.0	1.0	3.0
Hispanic/Chicano/Latino	5.7	0.2	3.0
Native American/Indian	0.7	0.5	0.6
Oriental/Asian	2.9	2.2	2.5
White/Caucasian	80.5	94.9	87.6
Mixed race	2.4	0.2	1.3
Other	1.2	0.2	0.7
Decline to answer	1.7	0.7	1.2
Religious Affiliation			
Catholic	24.9	22.7	23.9
Jewish	3.8	10.0	6.9
Mainline Protestant	13.3	26.2	19.6
Evangelical Protestant	7.6	11.0	9.3
Other	19.7	7.6	13.7
Not affiliated	25.4	19.1	22.3
Decline to answer	5.2	3.4	

Table 4-2: Sample Description (2 of 2)

	Group %		
	Nonelderly	**Elderly**	**Total**
	n = 409	*n* = 421	*n* = 830
Employment Status			
Employed full-time	62.9	4.6	34.2
Employed part-time	10.7	9.8	10.2
Not employed but looking for work	2.4	0.7	1.6
Not employed, not looking for work	0.7	0.2	0.5
Not employed, disabled	1.2	0.5	0.8
Retired	10.9	80.7	45.3
Student	2.4	0.2	1.3
Homemaker/housewife	8.3	2.2	5.3
Other	0.5	1.0	0.7
Education Status			
Some high school or less	0.2	0.5	0.4
High school graduate	10.5	9.3	9.9
Some college	20.0	21.0	20.5
2-year college/technical school graduate	13.3	9.5	11.4
4-year college graduate	23.5	24.4	24.0
Some postgraduate work	8.6	9.0	8.8
Postgraduate degree	24.0	26.2	25.1
Household Income			
Under $15,000	0.7	0.5	.6
$15,000 – $24,999	2.4	1.2	1.8
$25,000 – $34,999	6.9	10.0	8.4
$35,000 – $44,999	15.9	9.5	12.8
$45,000 – $74,999	31.1	38.9	34.9
$75,000 – $99,999	17.6	19.3	18.4
$100,000 – $149,999	15.9	9.0	12.5
$150,000 or more	6.2	5.6	5.9
Decline to answer	0.7	0.5	4.6

Table 4-3: Demographic Means

	Group Mean		
	Nonelderly	**Elderly**	**Total**
	n = 409	*n* = 421	*n* = 830
Age	47.5	70.7	59.0
# prescriptions purchased at the pharmacy in the past year	13.3	19.1	16.2
# total persons live in household	2.42	1.85	2.1

Table 4-4: Non-response Bias Categorical Analysis Elderly Segment Sample Description (1 of 2)

Variable	***First 10%*** ***(n=41)***	***Last 10%*** ***(n=42)***	χ^2 ***p-value***
Gender			0.105 0.75
Men	21 (51%)	23 (55%)	
Women	20 (49%)	19 (45%)	
Marital Status			5.15 0.398
Single, never married	1 (2%)	1 (2%)	
Unmarried couple living together	0 (0%)	3 (7%)	
Married	27 (66%)	28 (67%)	
Separated	0 (0%)	1 (2%)	
Divorced	4 (10%)	4 (10%)	
Widowed	9 (22%)	5 (12%)	
Decline to answer			
Race			4.00 0.406
Black/African American	1 (2%)	0 (0%)	
Hispanic/Chicano/Latino	0 (0%)	1 (2%)	
Oriental/Asian	0 (0%)	1 (2%)	
White/Caucasian	39 (95%)	40 (95%)	
Other	1 (2%)	0 (0%)	
Religious Affiliation			9.93 0.08
Catholic	7 (17%)	15 (36%)	
Jewish	3 (7%)	5 (12%)	
Mainline Protestant	15 (37%)	13 (31%)	
Evangelical Protestant	4 (10%)	4 (10%)	
Other	3 (7%)	3 (7%)	
Not affiliated	9 (22%)	2 (5%)	

Table 4-5: Non-response Bias Categorical Analysis Elderly Segment Sample Description (2 of 2)

Variable	*First 10%* *(n=41)*	*Last 10%* *(n=42)*	χ^2 *p-value*
Employment Status			3.62 0.460
Employed full-time	1 (2%)	0 (0%)	
Employed part-time	2 (5%)	5 (12%)	
Not employed, disabled	1 (2%)	0 (0%)	
Retired	35 (85%)	36 (86%)	
Homemaker/housewife	2 (5%)	1 (2%)	
Education Status			4.03 0.546
High school graduate	7 (17%)	3 (7%)	
Some college	5 (12%)	6 (14%)	
2-year college/technical school graduate	1 (2%)	4 (10%)	
4-year college graduate	14 (34%)	12 (29%)	
Some postgraduate work	4 (10%)	4 (10%)	
Postgraduate degree	10 (24%)	13 (31%)	
Household Income			14.3 0.075
Under $15,000	1 (2%)	0 (0%)	
$15,000 – $24,999	1 (2%)	0 (0%)	
$25,000 – $34,999	9 (22%)	1 (2%)	
$35,000 – $44,999	4 (10%)	1 (2%)	
$45,000 – $74,999	11 (27%)	20 (48%)	
$75,000 – $99,999	6 (15%)	10 (24%)	
$100,000 – $149,999	4 (10%)	3 (7%)	
$150,000 or more	2 (5%)	3 (7%)	
Decline to answer	3 (7%)	4 (10%)	

Table 4-6: Non-response Bias Continuous Analysis Elderly Segment

Variable	*Mean and Std Error*	*First 10% (n=41)*	*Last 10% (n=42)*	*t-value*	*p-value*
Age	mean	72.3	70.4	1.73	0.088
	std error	0.89	0.59		
# prescriptions purchased at the pharmacy in the past year	mean	20.39	21.71	-0.18	0.855
	std error	5.18	5.07		
# total persons live in household	mean	1.78	1.88	-0.73	0.465
	std error	0.76	0.45		
FDA trust	mean	3.13	3.04	0.654	0.515
	std error	0.098	0.098		
Trust in physician	mean	2.55	2.49	0.360	0.720
	std error	0.120	0.100		
Beliefs about the drug	mean	4.81	4.78	0.138	0.890
	std error	0.169	0.161		
Involvement in medical decision making	mean	2.77	2.92	-1.06	0.294
	std error	0.101	0.098		
Initial compliance	mean	5.76	6.17	-1.55	0.125
	std error	0.184	0.185		
Relevance and reliability of information from physician	mean	3.61	3.56	0.117	0.907
	std error	0.294	0.275		

Exploratory factor analysis was run on the following six scales:

1. FDA trust
2. Trust in physician
3. Beliefs about the drug
4. Involvement in medical decision making
5. Initial compliance intention
6. Relevance and reliability of drug information from physician.

For the FDA trust scale, a single factor solution was obtained which accounted for 67.6% of variance. The factor loadings for the single component are shown in Table 4-11.

Table 4-7: Non-response Bias Categorical Analysis Non-Elderly Segment Sample Description (1of 2)

Variable	*First 10%* *(n=42)*	*Last 10%* *(n=43)*	χ^2 *p-value*
Gender			0.72 0.397
Men	12 (29%)	16 (37%)	
Women	30 (71%)	27 (63%)	
Marital Status			5.13 0.400
Single, never married	6 (14%)	7 (16%)	
Unmarried couple living together	5 (12%)	2 (5%)	
Married	27 (64%)	24 (56%)	
Divorced	3 (7%)	7 (16%)	
Widowed	0 (0%)	2 (5%)	
Decline to answer	1 (2%)	1 (2%)	
Race			3.04 0.803
Black/African American	0 (0%)	1 (2%)	
Hispanic/Chicano/Latino	3 (7%)	3 (7%)	
Oriental/Asian	1 (2%)	1 (2%)	
White/Caucasian	35 (83%)	37 (86%)	
Mixed race	1 (2%)	1 (2%)	
Other	1 (2%)	0 (0%)	
Decline to answer	1 (2%)	0 (0%)	
Religious Affiliation			7.37 0.288
Catholic	8 (19%)	13 (30%)	
Jewish	2 (5%)	1 (2%)	
Mainline Protestant	2 (5%)	7 (16%)	
Evangelical Protestant	5 (12%)	3 (7%)	
Other	7 (17%)	9 (21%)	
Not affiliated	15 (36%)	8 (19%)	
Decline to answer	3 (7%)	2 (5%)	

Table 4-8: Non-response Bias Categorical Analysis Non-Elderly Segment Sample Description (2 of 2)

Variable	*First 10% (n=42)*	*Last 10% (n=43)*	χ^2 *p-value*
Employment Status			12.4 0.054
Employed full-time	26 (62%)	25 (58%)	
Employed part-time	5 (12%)	4 (9%)	
Not employed but looking for work	2 (5%)	0 (0%)	
Not employed, disabled	1 (2%)	0 (0%)	
Retired	1 (2%)	8 (19%)	
Student	1 (0%)	4 (9%)	
Homemaker/housewife	6 (14%)	2 (5%)	
Education Status			4.78 0.444
High school graduate	5 (12%)	3 (7%)	
Some college	4 (10%)	9 (21%)	
2-year college/technical school graduate	7 (17%)	10 (23%)	
4-year college graduate	14 (33%)	9 (21%)	
Some postgraduate work	3 (7%)	5 (12%)	
Postgraduate degree	9 (21%)	7 (16%)	
Household Income			5.66 0.685
Under $15,000	0 (0%)	1 (2%)	
$15,000 – $24,999	0 (0%)	1 (2%)	
$25,000 – $34,999	3 (7%)	1 (2%)	
$35,000 – $44,999	4 (10%)	8 (19%)	
$45,000 – $74,999	15 (36%)	16 (37%)	
$75,000 – $99,999	8 (19%)	6 (14%)	
$100,000 – $149,999	7 (17%)	4 (9%)	
$150,000 or more	2 (5%)	3 (7%)	
Decline to answer	3 (7%)	3 (7%)	

Table 4-9: Non-response Bias Continuous Analysis Elderly Segment

Variable	*Mean and Std Error*	*First 10% (n=42)*	*Last 10% (n=43)*	*t-value*	*p-value*
Age	mean	46.1	50.8		
	std error	1.84	1.84	-1.67	0.099
# prescriptions purchased at the pharmacy in the past year	mean	12.98	13.35		
	std error	3.27	1.8	-0.101	0.920
# total persons live in household	mean	2.64	2.65		
	std error	0.236	0.169	-0.029	0.977
Trust in physician	mean	2.74	2.79		
	std error	0.12	0.1	-0.36	0.72
Beliefs about the drug	mean	4.55	4.64		
	std error	0.131	0.152	-0.43	0.668
Involvement in medical decision making	mean	3.13	3.02		
	std error	0.064	0.087	1.07	0.288
Initial compliance	mean	5.44	5.79		
	std error	0.135	0.166	-1.64	0.106
Relevance and reliability of information from physician	mean	3.83	3.75		
	std error	0.21	0.244	0.249	0.804

Table 4-10: Cronbach's Alpha for Scales

Scale (n = 830)	# Items	Value
FDA trust	6	0.90
Trust in physician	5	0.87
Beliefs about the drug	8	0.83
Involvement in medical decision making	7	0.73
Initial compliance	4	0.92
Relevance and reliability of information from physician	8	0.97
Social desirability	10	0.63

Table 4-11: Factor Loadings for FDA Trust Scale

Items	Component
	1
The FDA is extremely thorough and careful.	.823
I completely trust the FDA's decisions about which medical treatments are safe and effective.	.894
The FDA would never mislead me about anything.	.844
Sometimes the FDA cares more about what is convenient for them than about the patients' medical needs.	.534
All in all, I trust the FDA completely.	.896
All in all, I trust completely in the FDA's ability to regulate prescription drugs.	.880

1 = Strongly Agree 5 = Strongly Disagree

For the trust in physician scale, a single factor solution was obtained which accounted for 66.0% of variance. The factor loadings for the single component are shown in Table 4-12.

Table 4-12: Factor Loadings for Trust in Physician Scale

Items	Component
	1
Sometimes this oncologist/allergist cares more about what is convenient for (him/her) than about your medical needs.	.669
This oncologist/allergist is extremely thorough and careful.	.823
You completely trust the oncologist/allergist's decisions about which medical treatments are best for you.	.877
This oncologist/allergist is totally honest in telling you about all of the different treatment options available for your condition.	.750
All in all, you have complete trust in this oncologist/allergist.	.917

1 = Strongly Agree 5 = Strongly Disagree

A two-factor solution was obtained for the drug belief scale which accounted for 76% of variance. The factor loadings for the two components are shown in Table 4-13.

A three factor solution was obtained for the involvement in medical decision making scale which accounted for 76% of variance. The factor loadings for the two components are shown in Table 4-14.

Table 4-13: Factor Loadings for Drug Belief Scale

Rotated Component Matrix		
Items	Component	
	1	2
Good	.758	.002
Favorable	.007	.906
Beneficial	.874	.004
Useful	.865	-.026
Effective	.907	-.025
Necessary	-.028	.905
Safe	.857	-.011
Helpful	.892	-.004

*7-point semantic scale

For the initial compliance intention scale, a single factor solution was obtained which accounted for 81.0% of variance. The factor loadings for the single component are shown in Table 4-15.

For the relevance and reliability scale, a single factor solution was obtained which accounted for 84.8% of variance. The factor loadings for the single component are shown in Table 4-16. Based on these loadings, all items were summed to form the scale.

Social Desirability Assessment

Pearson's correlation coefficient was used as the measure of association between the other scales and the Marlowe-Crowne Social Desirability Scale (Strahan and Gerbasi 1972), despite its low Cronbach's alpha (0.63). Although statistically significant, the apparent risk of

social desirability was deemed limited. Table 4-17 summarizes the findings of the scales' significant correlations ($p < 0.05$).

Table 4-14: Factor Loadings for Involvement in Medical Decision Making Scale

Rotated Component Matrix			
Items	Component		
	1	2	3
I will always follow this oncologist's/allergist's recommendations about treatment.	.775	.016	.230
It is better to rely on the expert judgment of this oncologist/allergist than to rely on common sense in taking care of my own body.	.587	.089	.560
It is better to seek professional help than to try to treat myself.	.135	.005	.908
Concerning my medical care, I should take complete control.	.013	.841	.186
Concerning my medical care, the oncologist/allergist should take complete control.	.789	.068	.135
In my future visits with the oncologist/allergist, I believe I will make all of the final decisions.	.197	.801	-.142
In my future visits with the oncologist/allergist, I believe the oncologist should take the initiative and decide what is best for me.	.826	.211	-.001

1 = Strongly Agree 5 = Strongly Disagree

Table 4-15: Factor Loadings for Initial Compliance Intention Scale

Items	Component
	1
No chance	.929
Likely	.813
Not possible	.943
Certain not to purchase	.910

*9-point semantic scale

Table 4-16: Factor Loadings for Relevance and Reliability Drug Information from Physician Scale

Items	Component
	1
Dependable	.914
Helpful	.936
Important	.888
Consistent	.908
Meaningful	.947
Relevant	.933
Reliable	.917
Useful	.924

*7-point semantic scale

Table 4-17: Social Desirability Scale Significant Correlations

Scale	*n*	Sig. (2-tailed)	Pearson's Correlation
Trust in physician	830	0.015	-0.085
Beliefs about the drug	830	0.002	.107

Trust in the FDA

The trust expressed in the FDA is weak at best and did not differ across age groups (Table 4-18). While there is slight agreement with the FDA being extremely thorough and careful (mean 2.61, standard deviation = 0.896), there is similar agreement that sometimes the FDA is more concerned about itself than about patients' medical needs (mean 2.73, standard deviation = 0.931).

General Beliefs of Off-Label Prescribing

The items in Table 4-19 were created to examine patient perceptions of off-label prescriptions, a current void in the off-label literature. Based on a five-point Likert scale, the reported means are close to the middle of the scale. Only three items had differences from the

midpoint greater than 0.5. Most respondents assumed (1) the majority of the prescriptions in the US were prescribed on-label (mean = 2.19, standard deviation = 0.696) and (2) most physicians

Table 4-18: Trust in FDA

	Nonelderly	Elderly	Total (*n* = 830)	
Item	Mean	Mean	Mean	SD
1. The FDA is extremely thorough and careful.	2.61	2.62	2.61	.896
2. I completely trust the FDA's decisions about which medical treatments are safe and effective.	2.93	2.94	2.93	.959
3. The FDA would never mislead me about anything.	3.17	3.20	3.19	.933
4. Sometimes the FDA cares more about what is convenient for them than about the patients' medical needs.	2.73	2.74	2.73	.931
5. All in all, I trust the FDA completely.	3.06	3.09	3.07	.960
6. All in all, I trust completely in the FDA's ability to regulate prescription drugs.	2.95	3.00	2.97	0.898

1 = Strongly Agree 5 = Strongly Disagree
*$p < 0.05$

knew whether the drug was FDA-approved for the indication for which it was prescribed (mean = 2.26, standard deviation = 0.782). Respondents believed their own prescriptions were FDA approved for the disease for which they use them (mean = 2.19, standard deviation = 0.898). There were statistically significant differences ($p<0.05$) among the elderly and nonelderly, with most differences revealing a tendency for younger respondents (1) to assume more use of off-label prescribing (items 1, 6, 12, and 13) and (2) potentially being more accepting of the concept and potential gains from off-label use (items 7, 8, and 9).

Manipulation Check

This study used a 2 × 2 × 2 design to assess the effects of off-label and on-label prescribing in two different levels of disease criticality and in two different norms of off-label

Table 4-19: General Beliefs of Off-Label Prescribing

	Nonelderly	Elderly	Total (n = 830)	
Item	Mean	Mean	Mean	SD
1. I believe the majority of prescriptions in the US are prescribed on label to treat diseases for which they are FDA approved.	2.25*	2.13*	2.19	0.696
2. I believe it is safe to use FDA-approved drugs off label to treat other diseases than for what they were originally approved.	2.76	2.76	2.76	0.838
3. I believe most physicians know when a drug is FDA approved or not approved to treat the disease in which they are prescribing it.	2.30	2.21	2.26	0.782
4. I believe insurance companies check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.	2.95	2.92	2.94	0.996
5. I believe pharmacists check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.	2.89	2.79	2.84	0.957
6. I believe all of the drugs I take are on label – FDA approved for the disease in which I use the drugs.	2.32*	2.06*	2.19	0.898
7. I believe drugs that are used on label – FDA approved for a disease – are always more effective than drugs that are not FDA approved for that disease.	3.06*	2.91*	2.99	0.892
8. I believe drugs that are on label – FDA approved for a disease – are always safer than drugs that are off label – not FDA approved for that disease.	2.93*	2.72*	2.83	0.917
9. I only want to be prescribed drugs that are on label – FDA approved to treat the specific disease I have.	2.85*	2.60*	2.73	0.994
10. I believe doctors who prescribe drugs off label for diseases for which the drugs are not FDA approved are superior doctors.	3.28	3.38	3.33	0.722
11. I believe only doctors who prescribe drugs off label – for diseases for which the drugs are not FDA approved – only do so because it is the best option for their patient.	2.63	2.62	2.62	0.812
12. I believe doctors only prescribe drugs off label – that are not FDA approved – for very rare diseases, not for more common ones.	3.01*	2.78*	2.90	0.868
13.For children, I believe doctors only prescribe drugs on label – for diseases for which the drugs are FDA approved.	2.72*	2.61*	2.66	0.839

1 = Strongly Agree 5 = Strongly Disagree

*$p < 0.05$

use based on the separation of beliefs between the diseases regarding potential harm and the negative impact on the respondent's life. As shown in Table 4-20, the disease criticality manipulation was determined to be effective.

Table 4-20: Disease Criticality Manipulation Check

After reading each statement, rate how much you agree or disagree with each statement. When answering these survey questions, I assume…	Disease	Mean	*n*	Std. Deviation
it is important to treat the ____ described in the scenario.	oncology	1.54*	412	0.716
	allergy	2.02*	418	0.687
the ___ described in the scenario will be extremely harmful to my health without the drug treatment.	oncology	1.60*	412	0.779
	allergy	3.04*	418	0.974
having the ___ described in the scenario will NOT have a large negative effect on my life.	oncology	4.03*	412	1.02
	allergy	2.67*	418	0.908

*Significance $p < 0.05$
1 = Strongly Agree 5 = Strongly Disagree

Research Questions and Propositions

The following section shows the results used to examine the study's 3 research questions, 13 propositions, and 2 hypotheses.

Research Question 1. What are the roles of disease criticality (DISCRIT), FDA approval status of the prescribed drug (FDASTAT), and the "normal" level of off-label use (OFFUSELVL) in beliefs formed about the prescribed drug, level of trust in the physician, level of involvement in medical decision making, and intentions of initial compliance?

Exploratory multiple regressions

Exploratory multiple regressions were used to measure the effects of disease state, normal level of FDA-approved product use, and FDA approval status on beliefs of the drug

initial compliance intent, trust in the physician, and involvement in medical decision making. The ability to model interactions, including two-way and three-way interactions, and identify issues such as multicollinearity was critical. The variables including interactions were all entered in one step, and the interactions were removed as they were found not to be significant.

Initial compliance intention

The relationships among the variables were first assessed with initial compliance as the dependent variable using the following equation:

Initial compliance = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

After it was revealed that the three-way interaction was not significant ($p > 0.05$), it was removed to assess the main effects and the two-way interactions. Neither interaction was significant; thus, they were removed to assess the main effects in the following equation:

Initial compliance = DISCRIT + OFFUSELVL + FDASTAT

Here the FDA status of the drug and the criticality of the disease were significant (Table 4-21), showing compliance was increased with on-label prescribing and in the more critical disease scenario.

Table 4-21. Main Effects Multiple Regression Model for Initial Compliance

	Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
	B	Std. Error	Beta		
(Constant)	5.705	.318		17.927	.000
DISCRIT	-.414	.120	-.116	-3.464	.001
OFFUSELVL	-.034	.120	-.010	-.286	.775
FDASTAT	.936	.120	.261	7.829	.000

Involvement in medical decision making

Involvement in medical decision making followed a pattern similar to the analysis of initial compliance after first using this equation to assess the interactions:

Involvement in medical decision making = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

The three-way interaction was not significant ($p > 0.05$) and was removed to assess the main effects and the two-way interactions. Neither interaction was significant; thus, they were removed to assess the main effects in the following equation:

Involvement in medical decision making = DISCRIT + OFFUSELVL + FDASTAT

Although the FDA status of the drug and the criticality of the disease were significant (Table 4-22), the relationship was the opposite direction as seen with initial compliance intention. Here an increase in involvement was observed with off-label prescribing and in the less critical disease scenario.

Table 4-22: Main Effects Multiple Regression Model for Involvement in Medical Decision Making

	Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
	B	Std. Error	Beta		
(Constant)	2.994	.102		29.236	.000
DISCRIT	.136	.039	.120	3.529	.000
OFFUSELVL	.016	.039	.014	.409	.683
FDASTAT	-.174	.038	-.154	-4.511	.000

Trust in Physician

The relationships among the variables were assessed with trust in the physician as the dependent variable using the following equation:

Trust in the physician = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

The three-way interaction was not significant ($p > 0.05$) and was removed to assess the main effects and the two-way interactions shown in the following equation:

Trust in the physician = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT

Here the FDASTAT*DISCRIT interaction was significant (Table 4-23) used in the final equation:

Trust in the physician = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*FDASTAT

Given the significance of the interaction, a step-down analysis examined the simple effects using *t* tests as shown in Table 4-24.

Table 4-23: Main Effects Multiple Regression Model for Trust in the Physician

	Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
	B	Std. Error	Beta		
(Constant)	2.304	.246		9.351	.000
DISCRIT	.449	.149	.323	3.014	.003
OFFUSELVL	.040	.047	.029	.847	.397
FDASTAT	.095	.149	.068	.632	.527
FDASTATXDISCRIT	-.249	.094	-.390	-2.637	.009

Table 4-24: Step-Down Analysis of Simple Effects (t tests) for Trust in the Physician

	t	Sig.	Means	
FDASTAT (off-label) DISCRIT	-2.92	.004	2.7 oncology	2.9 allergy
FDASTAT (on-label) DISCRIT	0.762	.446	2.5 oncology	2.5 allergy
DISCRIT (oncology) FDASTAT	2.214	.027	2.7 off-label	2.5 on-label
DISCRIT (allergy) FDASTAT	6.289	< 0.000	2.9 off-label	2.5 on-label

This shows the magnitude of the effect of off-label prescribing was moderated by the disease criticality. Respondents had a greater decrease in trust in the physician when receiving an off-label prescription in a less critical disease state than in a more critical disease state.

Belief measures about the drug

The relationships among the variables were assessed with trust in the physician as the dependent variable using the following equation:

Beliefs of the drug = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT + DISCRIT*OFFUSELVL*FDASTAT

The three-way interaction was not significant ($p > 0.05$) and was removed to assess the main effects and the two-way interactions shown in the following equation:

Beliefs of the drug = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*OFFUSELVL + DISCRIT*FDASTAT + OFFUSELVL*FDASTAT

Here the FDASTAT*DISCRIT interaction was significant (Table 4-25) used in the final equation:

Beliefs of the drug = DISCRIT + OFFUSELVL + FDASTAT + DISCRIT*FDASTAT

Table 4-25: Main Effects Multiple Regression Model for Beliefs of the Drug

	Unstandardized Coefficients		Standardized Coefficients	*t*	Sig.
	B	Std. Error	Beta		
(Constant)	4.997	.410		12.191	.000
DISCRIT	-.489	.248	-.214	-1.973	.049
OFFUSELVL	.027	.078	.012	.346	.729
FDASTAT	-.107	.249	-.047	-.430	.668
FDASTATXDISCRIT	.317	.157	.303	2.023	.043

Given the significance of the interaction, a step-down analysis examined the simple effects using *t* tests as shown in Table 4-26.

Table 4-26: Main Effects Multiple Regression Model for Beliefs of the Drug

	t	Sig.	Means	
FDASTAT (off-label) DISCRIT	1.648	0.100	4.8 oncology	4.6 allergy
FDASTAT (on-label) DISCRIT	-1.237	0.217	5.0 oncology	5.1 allergy
DISCRIT (oncology) FDASTAT	-1.906	0.057	4.8 off-label	5.0 on-label
DISCRIT (allergy) FDASTAT	-4.757	< 0.000	4.6 off-label	5.1 on-label

This shows that the effect of off-label prescribing was moderated by the disease criticality. Respondents had a significant loss in beliefs in the drug when receiving an off-label prescription compared to on-label drug only in the less critical disease state (allergy).

Propositions 1- 12

In addition to being informed by the exploratory multiple regressions, simple *t* tests were used to determine if the 2 group means were different for each of the 12 research propositions.

P_1 The prescribing of an FDA-approved drug leads to a greater likelihood of patient initial compliance intention with a prescription than prescribing off-label.

As shown in the regression analysis, off-label prescribing did decrease the initial compliance intention. It was also assessed using a simple *t* test showing a significant greater compliance intention with an on-label prescription ($p < 0.000$). The additional support for Proposition 1 is displayed in Table 4-27.

Table 4-27: *T*-Test of Initial Compliance Intention* by FDA Approval Status

FDA Status	*n*	Mean	s.d.
Off-label	415	5.97	1.81
On-label	415	6.90	1.65

*9-point semantic scale

P_2 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to a lower likelihood of patient initial compliance with a prescription than prescribing an FDA-approved drug.

The simple *t* test showed a significant decrease in compliance intention with an off-label prescription ($p < 0.000$) when the norm (75%) was to use an on-label drug. The support for Proposition 2 is displayed in Table 4-28.

Table 4-28: *T*-Test of Initial Compliance Intention* by FDA Approval Status When Norm Is to Use On-Label

FDA Status	N	Mean	s.d.
Off-label	204	6.04	1.80
On-label	208	6.81	1.62

*9-point semantic scale

P_3 The prescribing of an off-label FDA-approved drug in a more critical disease leads to a greater likelihood of patient initial compliance with a prescription than in a less critical disease.

The simple *t* test showed a significant decrease in compliance intention with an off-label prescription ($p = 0.004$) in a less critical disease state. The support for Proposition 3 is displayed in Table 4-29.

Table 4-29: *T*-Test of Initial Compliance Intention* by Disease Criticality When Receiving Off-Label Prescription

Disease Criticality	*n*	Mean	s.d.
Oncology	206	6.22	1.87
Allergy	209	5.72	1.72

*9-point semantic scale

P_4 The prescribing of an FDA-approved drug leads to a greater trust in the physician than prescribing off-label.

As shown in the regression analysis, off-label prescribing did decrease trust in the physician; however, the relationship was shown to be colored by disease criticality as well. The proposition was also assessed using a simple *t* test showing a significant decrease in trust in the physician when writing an off-label prescription ($p < 0.000$). The additional support for Proposition 4 is displayed in Table 4-30.

Table 4-30: *T*-Test of Trust in Physician* by FDA Approval Status

FDA Status	*n*	Mean	s.d.
Off-label	415	2.76	0.70
On-label	415	2.48	0.66

*1 = Strongly Agree 5 = Strongly Disagree

P_5 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to lower trust in the physician than prescribing an FDA-approved drug.

The simple *t* test showed a significant decrease in trust in the physician with an off-label prescription ($p < 0.000$) when the norm (75%) was to use an on-label drug. The support for Proposition 5 is displayed in Table 4-31.

Table 4-31: *T*-Test of Trust in Physician* by FDA Approval Status When Norm Is to Use On-Label

FDA Status	*n*	Mean	s.d.
Off-label	204	2.77	0.74
On-label	208	2.51	0.66

*1 = Strongly Agree 5 = Strongly Disagree

P_6 The prescribing of an off-label FDA-approved drug in a less critical disease leads to a lower trust in the physician than in a more critical disease.

The simple *t* test showed a significant decrease in trust in the physician with an off-label prescription ($p = 0.004$) in a less critical disease state. The support for Proposition 3 is displayed in Table 4-32.

Table 4-32: *T*-Test of Trust in the Physician* by Disease Criticality When Receiving Off-Label Prescription

Disease Criticality	*n*	Mean	s.d.
Oncology	206	2.66	0.71
Allergy	209	2.86	0.69

*1=Strongly Agree 5 = Strongly Disagree

P_7 There is no difference in the likelihood of patient involvement in medical decision making when an FDA-approved drug is prescribed than when an off-label drug is prescribed.

The proposition was assessed using a simple *t* test showing a significant increase in patient involvement in medical decision making when writing an off-label prescription ($p < 0.000$). The significant difference refutes Proposition 7 and is displayed in Table 4-33.

Table 4-33: *T*-Test of Patient Involvement in Medical Decision Making* by FDA Approval Status

FDA Status	*n*	Mean	s.d.
Off-label	415	3.05	0.54
On-label	415	2.88	0.57

*1 = Strongly Agree 5 = Strongly Disagree

P_8 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an FDA-approved drug when the norm is to use FDA-approved products than prescribing an off-label drug.

The simple *t* test showed a significant increase in involvement in medical decision making with an off-label prescription ($p = 0.010$) when the norm (75%) was to use an on-label drug. The significant difference refutes Proposition 8 and is displayed in Table 4-34.

Table 4-34: *T*-Test of Patient Involvement in Medical Decision Making* by FDA Approval Status When Norm Is to Use On-Label

FDA Status	*n*	Mean	s.d.
Off-label	211	3.02	0.52
On-label	207	2.89	0.56

1 = Strongly Agree 5 = Strongly Disagree

P_9 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an off-label drug in a critical disease than in a less critical disease.

The simple *t* test showed a significant increase in involvement in medical decision making with an off-label prescription ($p = 0.001$) in a less critical disease state. The significant difference refutes Proposition 9 and is displayed in Table 4-35.

Table 4-35: *T*-Test of Patient Involvement in Medical Decision Making* by Disease Criticality When Receiving Off-Label Prescription

Disease Criticality	*n*	Mean	s.d.
Oncology	206	2.96	0.53
Allergy	209	3.14	0.54

*1=Strongly Agree 5 = Strongly Disagree

P_{10} The prescribing of an FDA-approved drug leads to stronger positive beliefs about the drug than prescribing off-label.

As shown in the regression analysis, off-label prescribing weakened beliefs in the drug, but only in the less critical disease. The proposition was also assessed using a simple *t* test showing significantly weakened beliefs in the drug when writing an off-label prescription ($p < 0.000$). The additional support for Proposition 10 is displayed in Table 4-36.

Table 4-36: *T*-Test of Beliefs About the Drug* by FDA Approval Status

FDA Status	*n*	Mean	s.d.
Off-label	415	4.67	1.07
On-label	415	5.04	1.19

*7-point semantic scale

P_{11} The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to weaker positive beliefs about the drug than prescribing an FDA-approved drug.

The simple *t* test showed a significant weakening of beliefs in the drug ($p < 0.000$) when the norm (75%) was to use an on-label drug. The support for Proposition 11 is displayed in Table 4-37.

Table 4-37: *T*-Test of Beliefs About the Drug* by FDA Approval Status When Norm Is to Use On-Label

FDA Status	*n*	Mean	s.d.
Off-label	211	4.60	1.05
On-label	207	5.08	1.15

*7-point semantic scale

P_{12} The prescribing of an off-label FDA-approved drug in a less critical disease leads to weaker positive beliefs about the drug than in a more critical disease.

The simple *t* test did not show a significant difference in beliefs in the drug with an off-label prescription ($p = .100$) in a less critical disease state. The significant difference refutes Proposition 9 and is displayed in Table 4-38.

Table 4-38: *T*-Test of Beliefs About the Drug* by Disease Criticality When Receiving Off-Label Prescription

Disease Criticality	*n*	Mean	s.d.
Oncology	206	4.76	1.10
Allergy	209	4.59	1.03

*7-point semantic scale

Research Question 2. What are the roles of relevance and reliability judgments of the physician-provided information in beliefs formed about a prescribed drug and the intentions of initial compliance?

H_1 The higher the judged relevance and reliability of the physician-provided information are, the stronger the positive beliefs formed about the prescription product will be.

H_2 The higher the judged relevance and reliability of the physician-provided information are, the greater the initial compliance intention will be.

A bivariate correlational analysis (Table 4-38) supported hypotheses 1 and 2. A significant Pearson's correlation coefficient ($p < 0.000$) demonstrated the association between the physician-provided information relevance and reliability and (1) beliefs about the medication and (2) initial compliance intention.

Table 4-39: Hypotheses 1 and 2 Correlation with Relevance and Reliability of MD Information*

Scale	*n*	Sig. (2-tailed)	Pearson's Correlation
Beliefs about the drug	830	< 0.000	0.510
Initial compliance intention	830	< 0.000	-0.601**

*7-point semantic scale
**Note: negative correlation is due to the reverse orientation of the scale

Research Question 3. How do the roles of these elements differ in a population of elderly patients when compared to younger patients?

The propositions below were tested using a series of independent *t* tests to identify age-related differences:

P_{13} Elderly (≥ 65 years old) patients differ from younger patients in responses to behavior of off-label use, trust in physicians, and initial compliance intentions.

P_{13oA} In the same off-label scenarios, elderly patients do not differ from younger patients in the strength of the beliefs formed about the prescription.

P_{13oB} In the same off-label scenarios, elderly patients do not differ from younger patients in their initial compliance intentions measured by a multi-item scale.

P_{13oC} In the same off-label scenarios, elderly patients do not differ from younger patients in their judgments of relevance and reliability of physician-provided information.

P_{13oD} In the same off-label scenarios, elderly patients do not differ from younger patients in their trust in physicians.

P_{13oE} In the same off-label scenarios, elderly patients do not differ from younger patients in their involvement in medical decision making.

Based on the results shown in Table 4-40, it appears that the elderly (≥ 65 years old) do differ from the nonelderly (< 65 years old) on all variables tested. Proposition 13 is supported by all relevant variable analyses (Table 4-41). The elderly appear to be slightly more trusting of physicians and positive in their beliefs about drugs as well as have higher intentions of initial compliance based on the scenarios. The elderly had lower intentions of involvement in the medical decision making. The higher trust in the physician and lower intentions to be involved in the decision making were likely supported by the elderly finding the information from the physician more relevant and reliable.

Table 4-40: Final Proposition 13 Test Results

Variables Tested	Age	*n*	Mean	Std. Deviation
Beliefs about the drug[1]	Elderly	409	4.96*	1.20386
	Nonelderly	421	4.76*	1.07785
Initial compliance intention[2]	Elderly	409	5.91*	1.13382
	Nonelderly	421	5.73*	.97099
Relevance and reliability of physician-provided information[2]	Elderly	409	3.42*	1.73946
	Nonelderly	421	3.77*	1.54225
Trust in physicians[3]	Elderly	409	2.57*	.72111
	Nonelderly	421	2.67*	.66756
Involvement in medical decision making[3]	Elderly	409	2.87*	.59241
	Nonelderly	421	3.05*	.52163

*Significance $p < 0.05$
[1]7-point semantic scale
[2]7-point semantic scale
[3]1 = Strongly Agree 5 = Strongly Disagree

Table 4-41. Final Proposition 13 Summary

Proposition	Supported? (Y/N)
P_{13} Elderly (≥ 65 years old) patients differ from younger patients (< 65 years old) in responses to behavior of off-label use, trust in physicians, and initial compliance intentions.	Yes
P_{13oA} In the same off-label scenarios, elderly patients do not differ from younger patients in the strength of the beliefs formed about the prescription.	No
P_{13oB} In the same off-label scenarios, elderly patients do not differ from younger patients in their initial compliance intentions measured by a multi-item scale.	No
P_{13oC} In the same off-label scenarios, elderly patients do not differ from younger patients in their judgments of relevance and reliability of physician-provided information.	No
P_{13oD} In the same off-label scenarios, elderly patients do not differ from younger patients in their trust in physicians.	No
P_{13oE} In the same off-label scenarios, elderly patients do not differ from younger patients in their involvement in medical decision making.	No

Table 4-42 is a summary of the support for all of the study's propositions and hypotheses.

Table 4-42: Final Proposition (1-13)/Hypotheses (1-2) Support Summary

Proposition/Hypothesis	Supported? (Y/N)
P_1 The prescribing of an FDA-approved drug leads to a greater likelihood of patient initial compliance intention with a prescription than prescribing off-label.	Yes
P_2 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to a lower likelihood of patient initial compliance with a prescription than prescribing an FDA-approved drug.	Yes
P_3 The prescribing of an off-label FDA-approved drug in a more critical disease leads to a greater likelihood of patient initial compliance with a prescription than in a less critical disease.	Yes
P_4 The prescribing of an FDA-approved drug leads to a greater trust in the physician than prescribing off-label.	Yes
P_5 The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to lower trust in the physician than prescribing an FDA-approved drug.	Yes
P_6 The prescribing of an off-label FDA-approved drug in a less critical disease leads to a lower trust in the physician than in a more critical disease.	Yes
P_7 There is no difference in the likelihood of patient involvement in medical decision making when an FDA-approved drug is prescribed than when an off-label drug is prescribed.	No
P_8 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an FDA-approved drug when the norm is to use FDA-approved products than prescribing an off-label drug.	No
P_9 There is no difference in the likelihood of patient involvement in medical decision making when being prescribed an off-label drug in a critical disease than in a less critical disease.	No
P_{10} The prescribing of an FDA-approved drug leads to stronger positive beliefs about the drug than prescribing off-label.	Yes
P_{11} The prescribing of an off-label FDA-approved drug when the norm is to use FDA-approved products leads to weaker positive beliefs about the drug than prescribing an FDA-approved drug.	Yes
P_{12} The prescribing of an off-label FDA-approved drug in a less critical disease leads to weaker positive beliefs about the drug than in a more critical disease.	Yes
H_1 The higher the judged relevance and reliability of the physician-provided information are, the stronger the positive beliefs formed about the prescription product will be.	Yes
H_2 The higher the judged relevance and reliability of the physician-provided information are, the greater the initial compliance intention will be.	Yes
P_{13} Elderly ($\geq$ 65 years old) patients differ from younger patients ($<$ 65 years old) in responses to behavior of off-label use, trust in physicians, and initial compliance intentions.	Yes

CHAPTER V

DISCUSSION AND IMPLICATIONS

Off-label prescribing is common, especially in certain disease states (Radley et al. 2006, Peppercorn 2008, Soares 2005, Tarbarrok 2000, Bazzano 2009, Pathak et al. 2010), yet no research exists that assesses the effect of non-FDA-approved uses of pharmaceuticals on patient decision making. This study seeks to begin to fill that void. A survey using an online panel obtained 830 responses between 2 age groups, elderly (≥ 65) and nonelderly (< 65). This chapter discusses the findings and the implications of this study, which sought to understand the effects of off-label prescribing on patient decision making.

Off-Label Prescribing Beliefs and Trust in the FDA

In general, respondents did not have strong opinions regarding off-label use. The means remained close to the midpoint of the scales. The responses reveal that most assume the majority of prescriptions in the US were prescribed on-label and that most assume physicians know when the drug is FDA-approved for the indication for which it is prescribed. The respondents appear to believe their own prescriptions were FDA approved for the disease for which they use them (mean = 2.19). When respondents were asked about their beliefs that pharmacists and insurance companies were monitoring off-label use, the responses were neutral. Ignorance may be affecting their opinions and thus limiting the direction and magnitude. Similar results were found in the only research identified that looked at patient perceptions of off-label use. Lenk et

al. (2009) studied the parents of 51 healthy children and 43 children with renal disease in Germany. "Knowledge about the practise of off-label use [was] generally poor in both groups. Surprisingly, this [was] also true for the parents of children with chronic disease. Nine percent of the parents of chronically ill children and 20% of the parents of healthy children would refuse treatment with an off-label drug" (p. 1743).

There were statically significant differences between the elderly and nonelderly regarding their beliefs about off-label prescribing. Most differences revealed a tendency for younger respondents to (1) assume more use of off-label prescribing in general and (2) acknowledge the existence of potential gains of off-label use and be more accepting of the concept of off-label use.

Trust in the FDA was also measured with no demonstrated difference between the age groups. It is interesting to note how the items all scored around the midpoint, with no mean being greater than a distance of 0.5 away from the midpoint on a 5-point scale. Directionally there is trust in the FDA; however, this trust is weak at best. This is slightly different from what previous research has shown: despite 93% of patients being confident about the safety and effectiveness of drugs approved for use in the US, roughly one third to over one half feel negatively about how the FDA is doing its perceived job (Pricewaterhouse Coopers 2010, Harris Interactive 2008).

As with other results in the study, the magnitude of the off-label beliefs and trust in the FDA are not strong, but the directions are interesting and generally apply to the hypothesized behavior and conceptual framework set out in Chapter II.

Trust in Physicians

Some have described patient trust as "a collective good, similar to 'social capital,' that is necessary for an effective health care system" (Thom et al. 2004, p. 126). Trust in the physician can affect initial compliance via willingness to pay. Lower levels of trust in physician were associated with an increased likelihood of forgoing medications with higher out-of-pocket costs. Only in the context of low levels of trust in physicians did the researchers find an association with low income and cost-related adherence. Researchers concluded that a "trusting physician relationship may moderate the impact of cost pressures on patients' medication adherence. More generally, addressing noncost barriers to adherence may reduce rates of cost-related medication underuse" (Piette et al. 2005, p. 1749).

Despite the importance of trust in the health care system and the readily identifiable challenges an off-label prescription could potentially cause, no studies have measured the impact. In this study, the scale selected (Dugan et al. 2004) was specifically developed for measuring trust in an individual physician—not trust in the medical profession—so the impact of the off-label prescription could be directly attributed to the prescribing physician.

In the scenarios studied, off-label prescribing did significantly decrease trust in the physician. Disease critically moderated this relationship. Respondents had a greater decrease in trust in physicians when receiving an off-label prescription in a less critical disease state than in a more critical disease state. Off-label prescribing seems to have the potential for a costly impact on the health care system's "social capital," trust in the prescribing physician.

Given the gap that likely exists between the tested scenarios of cancer and allergies, one is left to question the relationship between off-label prescribing and less "urgent" diseases (e.g., hypertension) or diseases in which some patients have more "disease and treatment knowledge," such as sometimes found in rare diseases.

Involvement in Decision Making

Trachtenberg and colleagues (2005, p. 345) describe the challenging relationship between trust and involvement in medical decision making:

> Both patient trust and active patient involvement are desirable in their own right and because they are associated with improved health outcomes. Paradoxically, however, it might be thought that these 2 attributes are in sharp conflict.
>
> Patient trust might be more consistent with a deferential style of patient-physician interaction in which patients are passive, in contrast to assertive patient questioning or limitation of physician authority which might be indicative of patient distrust.

Their research with American adult patients (n = 533) found that the most significant predictor of patients' preferred role in medical decision making was trust in the medical profession (not the specific physician). Although that finding suggests that involvement in decision making may be independent of trust in the specific physician, it seems that when trust was reduced in the prescribing scenarios, involvement in decision making increased at least temporarily. The involvement increase with off-label prescribing was especially noted in the less critical disease scenario. This suggests that when patients perceive something is amiss or may go awry, they feel they must monitor it more closely, especially in a disease state for which they may have more knowledge (e.g., allergies versus cancer).

These results support previous research which found patients' desire to be involved in decision making and the treatment process to be inversely proportional to the disease criticality in numerous diseases (Levinson et al. 2005, Arora et al. 2000).

Belief About the Drug

In this study, univariate analysis showed a significant decrease in beliefs formed about the drug. A significant decrease in beliefs about the drug was observed in multivariate analysis when receiving an off-label prescription compared to on-label drug, but only in the less critical disease state (allergy). Further research is needed to understand the cause for this difference as well as means to avoid this lowering of beliefs. It should be noted that trust in the physician diminished significantly in both disease states, albeit more in allergies. Trust in the physician, therefore, was arguably put at greater risk with off-label prescribing than positive beliefs about the drug.

Positive beliefs about a drug have been shown to have positive correlations with compliance intentions (Lobb 2007). Thus, weakening these beliefs may have a deleterious impact on the health care system.

Initial Compliance Intention

The exact path of noncompliance is complex at a minimum, and the costs are potentially greater than $258.3 billion (Express Scripts 2010). Patients can deviate from the prescriber's instructions either volitionally or nonvolitionally. The deviation is volitional when the patient makes a conscious choice to be noncompliant with the instructions (Bentley et al. 1999). "[P]olypharmacy and poor patient–healthcare provider relationships (including the use of multiple providers) may be major determinants of nonadherence among older persons, with the impact of most sociodemographic factors being negligible" (Vik et al. 2004, p. 303). Off-label prescribing creates another opportunity for poor communications. In the scenarios studied, the linear regression revealed a direct relationship between off-label prescribing and a decrease in initial compliance intention. Unlike the impact on drug beliefs, this relationship was not

moderated by disease criticality or other variables. Across all scenarios, off-label use decreased initial compliance intentions by nearly a full point based on a nine-point scale (on-label mean = 6.90, off-label mean = 5.97, $p < 0.000$).

Given the emphasis placed on compliance, further research is needed to determine methods that diminish the negative impact on compliance of receiving on off-label prescription. Can a physician, nurse, or pharmacist simply avoid this decrease in compliance via a small verbal or written communication with the patient?

Relevance and Reliability Judgments

The role of relevance and reliability judgments in belief formation has been addressed in several studies (Sewak 2002, West et al. 2004, Jalnawala and Wilkin 2004, Lobb 2007, King and Wilkin 2004). Relevance judgments have been used by patients to assess the utility of the information and reliability judgments to assess the dependability of pharmacists (West et al. 2004).

A significant positive correlation ($p < 0.000$) demonstrated the association between the physician-provided information relevance and reliability and (1) beliefs about the medication (Pearson's correlation 0.510) and (2) initial compliance intention (Pearson's correlation 0.601). Thus, Hypothesis 1 and Hypothesis 2 were supported.

Elderly

The elderly (≥ 65 years old) did significantly differ from the nonelderly (< 65 years old) on virtually all measures except trust in the FDA. The elderly appear to be slightly more trusting of physicians and positive in their beliefs about drugs. This may have supported the higher relevant and reliability ratings in the elderly. Combined, these higher ratings among the elderly

likely led to the lower expressions of intentions of involvement in the medical decision making and the higher initial compliance intentions.

These significant differences ($p < 0.5$) must also be interpreted cautiously. When looking at the means, the greatest variation was ~0.25 on a 7-point scale or ~0.18 on a 5-point scale.

Limitations

An online consumer panel was used as the sample frame for this study. This panel may not represent the general population of the US and thus limits generalizability. The elderly group was 95% Caucasian/white, which is under representative of minorities in the general US population. It is important to note that while the exact percentages may not represent the population, the response patterns identified in this experimental design remain indicative of human behavior. Given the wide use of off-label prescribing, any incremental decrease in compliance or trust in the physician can have significant implications for the health care system.

The scenarios may also not represent reality. No studies have shown how often the FDA status of the drug is discussed with patients by physicians, pharmacists, or other health care professionals; however, these exchanges are likely taking place. The American Cancer Society (2011) Web site, with a section entitled, "What questions should I ask my physician about off-label drug use?" is evidence of these communications.

The definition and introductory paragraphs on off-label prescribing provided to respondents in this study may be more effective in communicating the concepts of on- and off-label prescribing than other available sources of information. There are many ways to handle the issue that were not covered in this study, including:

- Passing "the talk" off to another health care professional
- Referring patients to a Web site

- Ignoring the issue
- Deemphasizing it
- Offering proactive instructions (e.g., "Don't worry about the information that the pharmacist will give you with the prescription").

The compliance measure in this study only dealt with initial compliance. The duration and modification of impact of off-label prescribing remain unknown. How long does the heightened involvement last? In the study scenarios, patients were made aware of the off-label use and told that the physician uses it normally in patients like them. What would happen if patients found out at the pharmacy counter that the prescribed drug was being used off-label? What if they discovered this at home after the prescription was filled? Authoritative arguments (e.g., health care professional supportive statement of off-label use) may become less important over time as the patient gains experience with the product, as shown in similar research (West et al. 2003).

Only the outpatient prescription setting was modeled. Given the large volume of physician-administered drugs (e.g., oncolytics), research on the impact of delivery setting may also yield intriguing results.

This study only measured the physician as a source of information. Previous studies have shown different relevance/reliability scores based on the source of the information (Lobb 2007). One can also foresee the information-seeking process differing based on criticality of the disease, which was also shown to affect behavior in this study.

The study was limited to two disease states with no expressed differences in the safety and efficacy of the disease-specific therapies. One can readily see how a child's ear infection may be treated differently than an elderly person's hypertension. This study did not attempt to

assess the trade-offs likely to occur in decision making with different efficacy and safety ratios. These factors are further complicated by financial implications associated with the payment for prescriptions.

Future Research

Despite the common use of off-label prescribing, little is known regarding the impact on patient decision making. This research has provided a base for future research to address the following questions:

1. Does the decrease in trust in the physician change other behaviors?
2. Can methods be created to overcome the decrease in trust in physicians and initial compliance intention? Will they differ in effect by the health care professional involved?
3. Given the difference between shown between allergies and cancer, where is the line drawn on disease criticality and the related impacts of off-label prescribing?
4. How long is trust in the physician lost?
5. How long does the patient feel compelled to be more involvement in medical decision making?
6. For how may refills before off-label prescribing no longer affects compliance?
7. How does off-label use of physician-administered products impact patient decision making?
8. Do the elderly and non-elderly remain different in their behavior?

Conclusions

Off-label prescribing can potentially lead to deleterious effects on patients' health, including lower compliance, lower trust in physicians, and lower beliefs in the prescribed drug. Given how common this phenomenon is in drug prescribing (Radley et al. 2006, Peppercorn 2008, Tarbarrok 2000, Bazzano 2009, Pathak et al. 2010), the lack of knowledge of its impact is alarming.

In this study, the effects of off-label use were shown to be significant and far reaching. Based solely on the probability that legal paperwork will continue to increase in the health care setting, it is foreseeable that more patients may become aware of the approval status of their prescriptions. As found in this study, only a single stimulus is required for patients to modify their trust in their physician, their perceived need to be involved in the health care decision making, their benefit and risk perceptions of their prescribed drug, and their willingness to fill that first prescription.

Differences exist between the elderly and nonelderly in attitude toward off-label prescribing, and these differences may call for different interventions in select scenarios. Although more likely to express a desire to be involved in the health care decision making, the nonelderly segment did appear to be more open to the potential gains of using off-label drugs in the appropriate setting.

As shown in previous research (Sewak 2002, West et al. 2004, Jalnawala and Wilkin 2004, Lobb 2007, King and Wilkin 2004), judgments of the relevance/reliability of the information appear to filter which information is used to form beliefs about the drug and appear also to affect initial compliance intentions. This study grants additional support to the Model of Belief Processing.

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APPENDIX

Survey Instrument

<Screening questionnaire>

S1A--For patients ≥65 years of age

Are you signed up as a member of a Medicare Part D plan for prescription medications?

1. Yes
2. No **(TERMINATE)**

S1B---For patients <65 years of age

Do you have insurance which covers prescription medication?

1. Yes
2. No (**TERMINATE)**

S2. --- FOR BOTH AGE GROUPS

Have you purchased a prescription medication at a pharmacy in the last 12 months?

1. Yes
2. No **(TERMINATE)**

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<Background on FDA>

Please read the description below of the United States Food and Drug Administration (also referred to as the FDA) taken from the FDA website and describes what they do.

"FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health."

<FDA trust>

After reading each statement, rate how much you agree or disagree with each statement regarding the US Food and Drug Administration.

Please rate your agreement with the following statement:

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. The FDA is extremely thorough and careful.
2. I completely trust the FDA's decisions about which medical treatments are safe and effective.
3. The FDA would never mislead me about anything.
4. Sometimes the FDA cares more about what is convenient for them than about the patients' medical needs.
5. All in all, I trust the FDA completely.
6. All in all, I trust completely in the FDA's ability to regulate prescription drugs.

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<Definition of off-label>

This study will involve off-label prescribing — the prescription of a medication in a manner different from that approved by the FDA. In the United States, since 1962, in order for prescription drugs to be allowed in the market, they must been proven safe and effective when treating the disease states that are listed in each drug's label, or **on label**. One previous FDA leader simplified the meaning of an FDA approval by saying something similar to this: FDA approval means if the drug is used in the right patients, in the right way, at the right dose, then the benefits outweigh the risks.

However, once approved by the FDA and marketed in the United States, doctors can legally rely on their professional judgment to use these FDA approved products to treat different diseases, even if those uses are not specifically approved by the FDA. This is called **off-label** use.

<Off-label attitudes>

After reading each statement, rate how much you agree or disagree with each statement.
Strongly Agree Agree Neutral Disagree Strongly Disagree

1. I believe the majority of prescriptions in the US are prescribed on label to treat diseases for which they are FDA approved.

2. I believe it is safe to use FDA approved drugs off label to treat other diseases than for what they were originally approved.

3. I believe most physicians know when a drug is FDA approved or not approved to treat the disease in which they are prescribing it.

4. I believe insurance companies check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.

5. I believe pharmacists check to make sure the drug prescribed by the physician is being used on label to treat a disease for which it has been FDA approved.

6. I believe all of the drugs I take are on label - FDA approved for the disease in which I use the drugs.

7. I believe drugs that are used on label - FDA approved for a disease - are always more effective than drugs that are used off label - FDA approved for that disease.

8. I believe drugs that are on label - FDA approved for a disease are always safer than drugs that are off label - not FDA approved for that disease.

9. I only want to be prescribed drugs that are on label - FDA approved to treat the specific disease I have.

10. I believe doctors who prescribe drugs off label for diseases for which the drugs are not FDA approved are superior doctors.

11. I believe doctors who prescribe drugs off label - for diseases for which the drugs are not FDA approved - only do so because it is the best option for their patient.

12. I believe doctors only prescribe drugs off label – for diseases for which the drugs are not FDA approved - for very rare diseases, not for more common ones.

13. For children, I believe doctors only prescribe drugs on label – for diseases for which the drugs are FDA approved.

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<Study>

The following section is going to ask you to imagine yourself in a situation when you are sick. Please read the description and answer the questions as if this situation had happened to you personally.

400 respondents ≥65 targeted for Scenarios 1 - 8 (50 each)
400 respondents <65 targeted for Scenarios 9 - 16 (50 each)

<Show 1 of 8 scenarios based on 2 age groups>

Scenario 1 (age ≥65 / oncology / 75% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients who may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are not approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug is **not** approved by the FDA for this type of cancer. However, I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 2 (age ≥65 / oncology / 75% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients who may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are not approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of cancer. I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 3 (age ≥65 / oncology / 25% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients who may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are not approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug is **not** approved by the FDA for this type of cancer. However, I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 4 (age ≥65 / oncology / 25% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients who may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are not approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of cancer. I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 5 (age ≥65 / allergy / 75% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are not approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is not** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergies and it has been very effective and safe."

Scenario 6 (age ≥65 / allergy / 75% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are not approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 7 (age ≥65 / allergy / 25% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are not approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is not** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 8 (age ≥65 / allergy / 25% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your Medicare helps cover the costs of the doctor visits and you have a Medicare Part D plan that helps cover the costs of medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are not approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 9 (age <65 / oncology / 75% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients that may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are not approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug is **not** approved by the FDA for this type of cancer. However, I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 10 (age <65 / oncology / 75% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients that may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are not approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of cancer. I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 11 (age <65 / oncology / 25% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients that may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are not approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug is **not** approved by the FDA for this type of cancer. However, I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 12 (age <65 / oncology / 25% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After several weeks of feeling a lack of energy, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an oncologist (a doctor that specializes in treating cancer). Your doctor said, "This oncologist is a good doctor to whom I send all my patients that may have cancer." The oncologist runs several tests and informs you that you have a rare form of blood cancer that affects your red blood cells and explains why your energy was low. If untreated, the cancer will very likely lead to death in the next year or so. The drugs normally used to treat this cancer are ones that can be taken daily at home, by mouth, for roughly 6 months.

The oncologist tells you national surveys show **75%** of the patients in the US with this type of cancer receive drugs that **are not approved** by the FDA to treat this type of cancer. The other **25%** receive drugs that **are approved** by the FDA to treat this type of cancer.

The oncologist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of cancer. I use this to treat all of my patients with this type of cancer and it has been very effective and safe."

Scenario 13 (age <65 / allergy / 75% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are not approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is not** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 14 (age <65 / allergy / 75% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of receive drugs that **are approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are not approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 15 (age <65 / allergy / 25% on label / off label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are not approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is not** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

Scenario 16 (age <65 / allergy / 25% on label / on label rx)

Assume that you are the following patient and you are experiencing the symptoms and events described. Your insurance helps cover the costs of doctor visits as well as your medications. After a few weeks of dealing with a runny nose and other small allergy issues, you sought care from your primary care doctor. After blood tests, your doctor said you need to go see an allergist (a doctor that specializes in treating allergies). Your doctor said, "This allergist is a good doctor to whom I send all my patients with allergies." The allergist runs several tests and informs you that you have a common form of allergy. If untreated, the allergy will continue to bother you with a runny nose and other small allergy issues. The drugs normally used to treat this allergy are ones that can be taken daily at home, by mouth, for roughly 6 months.

The allergist tells you national surveys show 75% of the patients in the US with this type of allergy receive drugs that **are not approved** by the FDA to treat this type of allergy. The other 25% receive drugs that **are approved** by the FDA to treat this type of allergy.

The allergist writes you a prescription for a drug and says, "This drug **is** approved by the FDA for this type of allergy. I use this to treat all of my patients with this type of allergy and it has been very effective and safe."

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<Trust in Physicians> SCENARIOS 1-4 and 9-12

After reading each statement, rate how much you agree or disagree with each statement:

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. Sometimes this oncologist cares more about what is convenient for (him/her) than about your medical needs.

2. This oncologist is extremely thorough and careful.

3. You completely trust the oncologist's decisions about which medical treatments are best for you.

4. This oncologist is totally honest in telling you about all of the different treatment options available for your condition.

5. All in all, you have complete trust in this oncologist.

< Trust in Physicians> SCENARIOS 5-8 and 13-16

After reading each statement, rate how much you agree or disagree with each statement:

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. Sometimes this allergist cares more about what is convenient for (him/her) than about your medical needs.

2. This allergist is extremely thorough and careful.

3. You completely trust the allergist's decisions about which medical treatments are best for you.

4. This allergist is totally honest in telling you about all of the different treatment options available for your condition.

5. All in all, you have complete trust in this allergist.

PAGE BREAK

<Relevance and reliability> SCENARIOS 1-4 and 9-12

In this scenario, I believe the information provided by the oncologist is:

Dependable	1	2	3	4	5	6	7	8	9	Undependable

Helpful	1	2	3	4	5	6	7	8	9	Not helpful
Important	1	2	3	4	5	6	7	8	9	Unimportant
Consistent	1	2	3	4	5	6	7	8	9	Inconsistent
Meaningful	1	2	3	4	5	6	7	8	9	Meaningless
Relevant	1	2	3	4	5	6	7	8	9	Irrelevant
Reliable	1	2	3	4	5	6	7	8	9	Unreliable
Useful	1	2	3	4	5	6	7	8	9	Useless

<Relevance and reliability> SCENARIOS 5-8 and 13-16

In this scenario, I believe the information provided by the allergist is:

Dependable	1	2	3	4	5	6	7	8	9	Undependable
Helpful	1	2	3	4	5	6	7	8	9	Not helpful
Important	1	2	3	4	5	6	7	8	9	Unimportant
Consistent	1	2	3	4	5	6	7	8	9	Inconsistent
Meaningful	1	2	3	4	5	6	7	8	9	Meaningless
Relevant	1	2	3	4	5	6	7	8	9	Irrelevant
Reliable	1	2	3	4	5	6	7	8	9	Unreliable
Useful	1	2	3	4	5	6	7	8	9	Useless

PAGE BREAK

<Patient involvement in medical decision making> SCENARIOS 1-4 and 9-12

After reading each statement, rate how much you agree or disagree with each statement regarding the scenario you just read.

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. I will always follow this oncologist's recommendations about treatment.
2. It is better to rely on the expert judgment of this oncologist's than to rely on common sense in taking care of my own body.
3. It is better to seek professional help than to try to treat myself.
4. Concerning my medical care, I should take complete control
5. Concerning my medical care, the oncologist should take complete control.
6. In my future visits with the oncologist, I believe I will make all of the final decisions.

7. In my future visits with the oncologist, I believe the oncologist should take the initiative and decide what is best for me.

<Patient involvement in medical decision making> SCENARIOS 5-8 and 13-16

After reading each statement, rate how much you agree or disagree with each statement regarding the scenario you just read.

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. I will always follow this allergist's recommendations about treatment.
2. It is better to rely on the expert judgment of this allergist's than to rely on common sense in taking care of my own body.
3. It is better to seek professional help than to try to treat myself.
4. Concerning my medical care, I should take complete control
5. Concerning my medical care, the allergist should take complete control.
6. In my future visits with the allergist, I believe I will make all of the final decisions.
7. In my future visits with the allergist, I believe the allergist should take the initiative and decide what is best for me.

PAGE BREAK

< Filling the prescription> SCENARIOS 1-4 and 9-12

You take your prescription from the oncologist to the pharmacy to be filled. The pharmacist fills the prescription and hands you the prescription. The pharmacist tells you that the prescription copayment is similar to other prescriptions you have received in the past.

I believe that the drug I have been prescribed is:

Bad	1	2	3	4	5	6	7	Good
Favorable	1	2	3	4	5	6	7	Unfavorable
Harmful	1	2	3	4	5	6	7	Beneficial
Useless	1	2	3	4	5	6	7	Useful
Ineffective	1	2	3	4	5	6	7	Effective
Necessary	1	2	3	4	5	6	7	Unnecessary
Dangerous	1	2	3	4	5	6	7	Safe
Not helpful	1	2	3	4	5	6	7	Helpful

Valuable	1	2	3	4	5	6	7	Not valuable
Expensive	1	2	3	4	5	6	7	Cheap
Worth the cost	1	2	3	4	5	6	7	Not worth the cost

< Filling the prescription> SCENARIOS 5-8 and 13-16

You take your prescription from the allergist to the pharmacy to be filled. The pharmacist fills the prescription and hands you the prescription. The pharmacist tells you that the prescription copayment is similar to other prescriptions you have received in the past.

I believe that the drug I have been prescribed is:

Bad	1	2	3	4	5	6	7	Good
Favorable	1	2	3	4	5	6	7	Unfavorable
Harmful	1	2	3	4	5	6	7	Beneficial
Useless	1	2	3	4	5	6	7	Useful
Ineffective	1	2	3	4	5	6	7	Effective
Necessary	1	2	3	4	5	6	7	Unnecessary
Dangerous	1	2	3	4	5	6	7	Safe
Not helpful	1	2	3	4	5	6	7	Helpful
Valuable	1	2	3	4	5	6	7	Not valuable
Expensive	1	2	3	4	5	6	7	Cheap
Worth the cost	1	2	3	4	5	6	7	Not worth the cost

PAGE BREAK

Based on the information available in this scenario, how likely are you to purchase this prescribed drug?

No chance	1	2	3	4	5	6	7	8	9	Sure to purchase
Likely	1	2	3	4	5	6	7	8	9	Unlikely
Not possible	1	2	3	4	5	6	7	8	9	Very possible
Certain not to purchase	1	2	3	4	5	6	7	8	9	Certain to purchase

PAGE BREAK

In this scenario, I believe the FDA approval of the prescribed drug is:

Dependable	1	2	3	4	5	6	7	8	9	Undependable
Helpful	1	2	3	4	5	6	7	8	9	Not helpful
Important	1	2	3	4	5	6	7	8	9	Unimportant
Consistent	1	2	3	4	5	6	7	8	9	Inconsistent
Meaningful	1	2	3	4	5	6	7	8	9	Meaningless

Relevant	1	2	3	4	5	6	7	8	9	Irrelevant
Reliable	1	2	3	4	5	6	7	8	9	Unreliable
Useful	1	2	3	4	5	6	7	8	9	Useless

PAGE BREAK

What is the typical copayment you pay for a month's supply of a drug? If unsure, please provide your best estimate.
$[_|_|._|_]

What would you be willing to pay for a month's supply of this drug?

$[_|_|._|_]

PAGE BREAK

<Manipulation check>

After reading each statement, rate how much you agree or disagree with each statement:

SCENARIOS 1-4 and 9-12 ONCOLOGY

Strongly Agree Agree Neutral Disagree Strongly Disagree

1. When answering these survey questions, I assume it is important to treat the cancer described in the scenario.

2. When answering these survey questions, I assume the cancer described in the scenario will be extremely harmful to my health without the drug treatment.

3. When answering these survey questions, I assume having the cancer described in the scenario will NOT have a large negative effect on my life.

SCENARIOS 5-8 and 13-16 ALLERGIES

1. When answering these survey questions, I assume it is important to treat the allergy described in the scenario.

2. When answering these survey questions, I assume the allergy described in the scenario will be extremely harmful to my health without the drug treatment.

3. When answering these survey questions, I assume having the allergy described in the scenario will NOT have a large negative effect on my life.

<Disease experience>

Have you ever been treated for cancer?

1. Yes
2. No
3. Decline to answer

Have you ever been treated for allergies?

1. Yes
2. No
3. Decline to answer

PAGE BREAK

After reading each statement, rate how much you agree or disagree with each statement.

Strongly Disagree	1	2	3	4	5	6	7	Strongly Agree

1. I always try to practice what I preach.

2. There have been occasions when I took advantage of someone.

3. I have never been irked when people expressed ideas very different from my own.

4. At times I have really insisted on having things my own way.

5. I am always willing to admit it when I make a mistake.

6. I like to gossip at times.

7. I never resent being asked to return a favor.

8. I sometimes try to get even rather than forgive and forget.

9. I have never deliberately said something that hurt someone's feelings.

10. There have been occasions when I felt like smashing things.

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<Demographics Part I>

Thank you for your interest in participating in our study about your health. We will begin by asking you some basic classification questions that will help us to customize the survey for you. Please be assured that all responses will remain confidential.

Are you…?

1. Male
2. Female

In what year were you born? (*Please enter as a four-digit number, e.g., 1970)*
[_|_|_|_]

How many prescriptions have you purchased at the pharmacy in the past year?
[_|_|_]

PAGE BREAK

<Demographics Part II >

What is your marital status?
[SINGLE RESPONSE]

1. Single, never married
2. Unmarried couple living together
3. Married
4. Separated
5. Divorced
6. Widowed
7. Decline to answer

Including yourself, how many people live in your household?
people in household [_|_]

What is the highest level of formal education you have completed?
[SINGLE RESPONSE]

1. Some high school or less
2. High school graduate
3. Some college
4. 2-year college/technical school graduate
5. 4-year college graduate
6. Some postgraduate work
7. Postgraduate degree

What is your race or ethnic heritage?
[SINGLE RESPONSE]

1. Black/African American
2. Hispanic/Chicano/Latino
3. Native American/Indian
4. Oriental/Asian
5. White/Caucasian
6. Mixed race
7. Other
8. Decline to answer

What is your primary religious affiliation?
[SINGLE RESPONSE]

1. Catholic
2. Jewish
3. Mainline Protestant
4. Evangelical Protestant
5. Other
6. Not affiliated
7. Decline to answer

What is your employment status?
[SINGLE RESPONSE]

1. Employed full-time
2. Employed part-time
3. Not employed but looking for work
4. Not employed, not looking for work
5. Not employed, disabled
6. Retired

7. Student
8. Homemaker/housewife
9. Other

What was your approximate total annual household income before taxes last year?
[SINGLE RESPONSE]

1. Under $15,000
2. $15,000-$24,999
3. $25,000-$34,999
4. $35,000-$44,999
5. $45,000-$74,999
6. $75,000-$99,999
7. $100,000-$149,999
8. $150,000 or more
9. Decline to answer

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<Debrief>

All of the information provided within this scenario about the diseases, percentages of off-label use, and drugs is fictitious.

VITA

Douglas Paul was born March 30, 1974, in Chesterfield, MO. After graduating from Parkway Central High School, he began his college education at the University of Mississippi, where he earned his PharmD in 1998. His Masters in Science in Pharmacy Administration was completed in 2005 at the University of Mississippi.

In 2001, he was a founding partner of Medical Marketing Economics. There he has worked on a variety of initiatives for pharmaceutical and medical technology companies, including marketing strategy, pricing strategy, pricing research, management/analysis of forecasts, market assessments, and the identification and evaluation of potential products for acquisition, joint marketing, and licensure. His research and consulting work has included ultra-orphan/orphan/biologic drug pricing.

He has been active at the national level with various pharmacy associations and played a key role in the development of the American College of Veterinary Pharmacists.