Determinants of Oral Medication Compliance in Osteoporosis: The Role of Medication Beliefs

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Chapter 1 - Introduction

The prevalence of chronic diseases such as osteoporosis continues to increase in concert with the age structure of the Unites States population. While non-medicinal approaches to manage these conditions are and will continue to be important, medications are often required to reduce the risk of adverse long-term health consequences of these diseases. Among those who are offered medication for osteoporosis or other chronic diseases, a substantial minority stop medication within a few months of the first prescription or exhibit sub-optimal compliance to them. Many factors have been shown to influence compliance, especially out of pocket drug cost, experience of side effects, the relationship with the prescribing provider, and perceived susceptibility to and seriousness of the target condition being treated. Other variables such as health value (the extent to which one values one's own health) locus of control, self-efficacy with respect to medication use, and social support regarding medication use may also play important roles in medication compliance among those with osteoporosis or other chronic diseases. Several qualitative studies, however, have suggested that a significant proportion of those with chronic illnesses have ambivalent or even outright negative attitudes toward medications, expressing concerns about dependency upon them and long-term risks (known and unknown) from their use.

Beliefs about medications are postulated as a potentially important factor influencing medication use behavior by several models of health behavior, including the Health Belief Model, the Theory of Planned Behavior, Protection Motivation Theory, and the Leventhal Self-Regulatory Model. At first glance, it appears obvious that positive or negative medication beliefs would influence medication use behavior. The degree to which beliefs about medications drive medication compliance, however, compared to other variables such as cost and the level of trust in the prescribing provider is unknown. For example, out of pocket drug cost may drive non-compliance even among those who do not have unfavorable attitudes toward their medications. A high level of trust in the prescribing physician may overtake negative or ambivalent attitudes regarding medications such that the patient is willing to suspend their ambivalent or negative beliefs and take medication as recommended, or patients may be more willing to adopt their physician's views of medications and target condition(s) they are used to treat if they have a higher level of trust in that provider. On the other hand, medication beliefs may be an important determinant of compliance even after

controlling for other important influences on compliance. In that case, programs designed to improve compliance may need to include direct solicitation of patients' beliefs about medications, assessment of the degree to which they are consistent with current knowledge about the target condition and the medication itself, and efforts to re-frame these beliefs to be more congruent with current knowledge regarding the medication itself, the patient's susceptibility to adverse consequences of the target condition, and the seriousness of those adverse consequences.

This dissertation is a detailed exposition of a cross-sectional survey and medical record review study to estimate the association of medication attitudes and self-reported use of fracture prevention medications among patients prescribed one organized into six chapters. This first chapter will first present a comprehensive review of the literature regarding the decision making process patients go through about whether or not to take medication that has been recommended to them by their provider, will highlight important gaps in current knowledge regarding medication compliance, and will conclude with a description of the specific research questions that this study will address.

The second chapter will present the original conceptual framework for the study, will review in detail the operationalization of the concepts within that framework, and will conclude with a principal components analysis of the items that were used to assess the latent variables within that framework to justify the operationalization of the latent constructs as separate variables.

Chapters 3 through 5 will each represent a paper addressing separate (albeit related) research questions. Chapter 6 will summarize the findings from these three papers, what knowledge gaps they address, and will describe a further program of research beyond this project to further address these knowledge gaps.

Background Literature Review

Medication Non-Compliance: Scope of the Problem

Medication prescribed to prevent adverse health events due to a chronic incurable target condition such as hypertension, hypercholesterolemia, type 2 diabetes mellitus, or osteoporosis typically need to be taken on a regular, ongoing basis in order to be effective. *Medication compliance* is defined as taking medication as recommended by the prescribing provider and dispensing pharmacist, presumably to

maximize its effectiveness and safety. This typically will include advice regarding how often to take the medication, whether or not doses need to be taken with or without food, whether or not doses need to be taken any particular time of the day, and whether or not any other activities should or should not be done at the time medication is actually taken.(1) Generally, the most common type of non-compliance is taking medication less often than what is necessary to achieve maximal benefit, although non-compliance in the form of inappropriate timing with respect to food or other activities and excessive use of medication do also occur. *Persistence* is defined as continuing with medication (even if in a non-adherent manner) and is the opposite of *discontinuation*, whereby use of a medication is stopped altogether.(1) Persistence generally has been operationally defined as failure to refill a prescription within some period of time after the last dispensing date.

Non-compliance and Non-Persistence with Medication to Treat Osteoporosis

Osteoporosis is a common condition of bone whereby loss of bone mass and microarchitectural deterioration of bone structure results in bone fragility and susceptibility to fracture.(2, 3) This is a common public health problem especially among the elderly of all ethnic groups, most notably Caucasian and Asian elderly. Among Caucasian women and men age 50, respectively, 40% and 13% can expect to have a fracture of the hip, wrist, or a vertebra sometime during their remaining lifetime.(4) These fractures can result in serious long-term health consequences. Only one-third of those who suffer a hip fracture recover their pre-fracture ability to ambulate,(5-7) and a substantial proportion of those who suffer vertebral fractures will have chronic back pain.(7-9) Symptomatic or clinical vertebral fractures cause height loss, and a 5-10% loss of lung vital capacity because of the resulting increased upward pressure on the diaphragm from abdominal organs.(10-12)

In the last 15 years, a variety of medications have become available that have been shown to reduce the risk of fractures 30 to 50%.(13-17) Guidelines promulgated by medical subspecialties such as the American Association of Clinical Endocrinologists(18) and the American College of Obstetrics & Gynecology(19) as well as professional societies specifically concerned with diagnosis and treatment of osteoporosis (such as the Canadian Osteoporosis Society(20) and the National Osteoporosis Foundation(21)) are in virtual unanimous agreement that medications to

reduce fracture risk are indicated in those with osteoporosis by bone density criteria, with a prevalent radiographic vertebral fracture, or a recent clinical fracture. Most prescriptions for fracture prevention therapy are medications in the bisphosphonate family. The two most commonly prescribed medications, alendronate and risedronate, are taken once weekly, and a less commonly used bisphosphonate, ibandronate, is taken once monthly. Hormone replacement therapy (HRT) is now used much less frequently for the primary purpose of fracture prevention, since the Women's Health Initiative study in 2002 documented increased risk of myocardial infarction, stroke, breast cancer, and thromboembolic disease associated with its use.(22) Raloxifene is a daily selective estrogen receptor modulator that is also FDA-approved for fracture prevention, but also is not generally used as a first line agent for fracture prevention because of its lack of efficacy with respect to preventing non-spine fractures.(16, 23) As is true with many other chronic diseases such as hypertension(24, 25) and hyperlipidemia,(26, 27) a substantial proportion of those prescribed medication to prevent osteoporosis stop medication prematurely, take it less frequently than prescribed, or take it inappropriately in some other manner.

Assessing compliance and persistence with fracture prevention medication using pharmacy claims databases

Recently, Kothawala and colleagues have performed a meta-analysis of observational studies that have assessed medication persistence and compliance to oral medication to prevent osteoporotic fracture.(28) The pooled persistence rate from the six studies that assessed persistence using pharmacy claims through 1 year from the index prescription was 50%. Thirteen studies assessed persistence by self-report, and among these the pooled estimated rate of persistence through 1 year of therapy was 80%. This meta-analysis included, however, studies of compliance with hormone replacement therapy and cyclical etidronate, an older bisphosphonate taken daily only for a two week period every 3 months that is no longer used for fracture prevention therapy.

A systematic review limited to 14 studies of compliance and persistence with oral bisphosphonate therapy assessed with large pharmacy claims databases estimated that persistence 1 year after an index prescription for a daily alendronate or risedronate ranged from 26% to 56%, and after an index prescription for a weekly

alendronate or risedronate ranged from 44% to 70%.(29) Generally, after new prescriptions for oral bisphosphonates, there is rapid drop of persistence over the first three months after the index prescription date, as many individuals will stop after filling one or two prescriptions, with a slower attrition of persistence with oral bisphosphonate therapy after that initial period.(30-37) Hence, rates of persistence will be lower one year after an index prescription for someone who has already been taking a bisphosphonate medication for 3 to 6 months, compared to new users.

In the largest of the pharmacy claims database studies done to date (using the NDCHealth pharmacy database of 14,000 retail pharmacies, identifying 211,319 individuals [47% over age 70] who filled a prescription for an oral bisphosphonate during the month of October, 2002) persistence at one year for new and established users of daily bisphosphonates, respectively, were 15.7% and 39%. Persistence at one year for new and established weekly oral bisphosphonate prescriptions, respectively, were 31% and 58%.(38) In this study, *compliance* for 1 year after the index prescription was defined as the Medication Possession Ratio (MPR), the proportion of days between refills for which the patient had medication in their possession. For new users (for whom there was no record of bisphosphonate use for the prior 12 months), only 25.2% of those starting a weekly bisphosphonate and 13.2% of those starting a daily bisphosphonate, respectively, achieved adequate compliance (defined as MPR $\geq$ 80%). Among existing users, the proportions achieving adequate compliance was somewhat better but still suboptimal, 48.1% and 35.2%, respectively, among weekly and daily bisphosphonate users. With one exception,(30) all of the oral bisphosphonate compliance studies done to date have shown that compliance and persistence with weekly bisphosphonates, although still suboptimal, is better than with daily bisphosphonates. However, here is no convincing evidence currently that persistence with once monthly ibandronate is any better than with weekly bisphosphonates.(39-41)

Although these large studies using pharmacy claims give a consistent description of the extent and time course of persistence and compliance with oral fracture prevention therapy, they are limited in that they can reliably assess only a few of the potential predictors of persistence and compliance, such as frequency of dosing, demographic variables, claims for co-morbid medical conditions, and claims for diagnostic tests such as bone densitometry and hence offer little in the way of explaining why individuals do or not persist and/or comply with prescriptions for

fracture prevention medication. Age in these studies is inconsistently associated with bisphosphonate persistence, as some have shown higher(36, 38, 42-45), lower(37), or no difference(35, 46) in persistence among patients older than age 65 to 75 compared to those of younger age. Having had a health care claim for a prior fracture is associated with slightly higher persistence,(37) as is having a claim for a bone density test within the two years prior to the index prescription.(30, 35, 37) Compliance appears to be better for those with third-party prescription coverage compared to those without prescription drug coverage,(38) and in a Canadian study, for those with public compared to those with private prescription drug coverage.(43) The association of a health care claim for a prior fracture before the index prescription date has been inconsistently associated with oral bisphosphonate persistence, being positively associated with persistence in some studies (36, 37) and not associated with persistence in others.(35, 44, 47) Concomitant prescription of a large number of medications is associated lower rates of persistence in most (35, 37) but not all studies.(48) and specifically concomitant prescriptions to reduce gastric acid secretion may be associated with lower oral bisphosphonate persistence,(45, 49) perhaps because these medications are used to treat gastric dyspepsia which sometimes may attributed to oral bisphosphonates. Interestingly, concomitant use of oral glucocorticoids medications are associated with *lower* persistence and/or compliance with oral bisphosphonate medications in some (35, 44) but not all studies.(47) In one study, current smoking was also associated with non-persistence.(49)

Assessing compliance and persistence with fracture prevention medication using survey methods

Several studies have assessed compliance to medications to prevent osteoporotic fracture using self-report surveys. Turbi and colleagues identified post-menopausal women prescribed medication for osteoporosis in 154 general practices across Spain, and compared self-reported compliance among 426 women prescribed weekly alendronate to compliance among 476 women prescribed daily raloxifene, a selective estrogen receptor modulator.(50) Compliance was assessed using the four item Morisky-Green scale, which ask respondents whether or not they sometimes miss medication doses due to forgetfulness, carelessness, when they are feeling better, or when they are feeling worse.(51) Sixty nine percent of patients prescribed raloxifene

and 54% of those prescribed alendronate, respectively, answered “no” to all items of the Morisky-Green scale, considered to be indicative of good compliance. The mean treatment duration was 324 days for raloxifene, and 291 days for alendronate. Participants prescribed raloxifene estimated that they remembered to take a mean 94% of all prescribed tablets, and those prescribed alendronate estimated that they took 90% of all prescribed tablets. A second set of investigators in Spain identified patients from 126 general practices who were being prescribed raloxifene, and randomized the 126 practices to either hand out a leaflet to study participants with additional information regarding raloxifene or to simply follow their usual practice.(52) Compliance was assessed by self-report with the Morisky-Green scale, with high compliance defined as all 4 items of the scale being answered “no”. High self-reported compliance was no different between the two groups, being 47.5% and 52.5%, respectively, in the intervention and no intervention groups after 12 months of follow-up. Quality of life assessed by self-report with the visual analog scale part of the EQ-5D was negatively associated with self-reported compliance in both groups.

Carnvale and colleagues surveyed over 2,000 Italian patients who suffered a hip fracture a mean 543 days before the survey date. Twenty one percent of those treated with a fracture prevention medication at the time of or immediately after the fracture self-reported stopping that medication by the time of the survey date. Performance of bone densitometry, younger age, and female sex were associated with fracture prevention medication persistence.(53)

Five studies have used surveys to assess both self-reported compliance to and persistence with osteoporosis medication, *and* reasons for discontinuation. Tosteson and colleagues conducted telephone surveys with 956 women prescribed medication to prevent osteoporotic fracture a mean 7 months after their first prescription. Twenty six percent, 19%, and 19%, respectively, of those prescribed hormone replacement therapy (HRT), raloxifene, or alendronate had discontinued therapy.(54) Among those discontinuing HRT, raloxifene, or alendronate, respectively, 59%, 42% and 49% reported very bothersome side effects. With all three medications, persistence with medication was more likely among those with an accurate recollection of their bone density test results. Similarly, among 275 consecutive post-menopausal women prescribed risedronate (another oral bisphosphonate) 42 of 48 patients who by self-report discontinued the medication cited one or more side effects as the reason for

discontinuation.(55) Two other studies, however, have suggested that side effects account for a lower percentage of premature discontinuation of osteoporosis medications. Of 310 post-menopausal women prescribed medication to prevent osteoporotic fracture following a bone density test, Pickney and colleagues reported that 150 self-reported discontinuation of the medication, and of those less than half cited side effects as the main reason.(56) Twenty six percent (26%) cited cost as the main reason for discontinuation. Side effects were also cited by a smaller proportion of patients as the main reason for discontinuation of osteoporosis medication prescribed to 9,851 post-menopausal women by several osteoporosis specialty centers across Italy.(57) Self-reported discontinuation rates over a mean follow-up time of 14 months (range 11-18 months) varied from just 6.9% for weekly alendronate to 23% for hormone replacement therapy, to 28.7% for intramuscular clodronate (administered once every 1-2 weeks). Persistence was positively associated with prior vertebral fractures, early menopause, and having had a bone density test showing low bone mass. Self-reported reasons for discontinuation were side effects in 24%, lack of motivation in 21%, safety concerns in 13%, and cost in 10%.

Uniquely among these studies, Cline and colleagues assessed the association of self-reported use of hormone replacement therapy or oral bisphosphonate medication within the month prior to the survey date with latent variables postulated to be associated with medication use by the Health Belief Model, specifically perceived susceptibility to osteoporosis, perceived severity (health consequences) of osteoporosis, perceived effectiveness of medications to treat osteoporosis, and perceived barriers to use of medications to treat osteoporosis.(58) Notably, the target condition was framed as “osteoporosis” and not specifically as osteoporotic fractures. This study also assessed type of health insurance coverage and “cues to action” (events or health history that indicate risk of osteoporosis or related fractures) such as having had a diagnosis of osteoporosis or osteopenia, family history of fracture, and a personal history of fracture. Having had a bone density test and having Medicare HMO health care coverage were both strongly associated with self-reported recent use of an anti-resorptive agent. Perceived susceptibility to osteoporosis, perceived effectiveness of drug therapy, and perceived lack of barriers to medication use were all modestly associated with self-reported recent use of anti-resorptive drug therapy.

Combined survey and pharmacy claims studies

Two studies have assessed fracture prevention medication using pharmacy claims, and have assessed a richer variety of potential predictors of medication use behavior using survey methods. Berecki-Gisolf surveyed 788 elderly Australian women who were filling a new prescription for an oral bisphosphonate medication, assessing health status with the SF-36, physical activity, smoking status, alcohol consumption, and dyspeptic symptoms. Age, marital status, self-reported ability to manage income, educational status, are of residence (rural versus urban), and SF-36 scores were unrelated to persistence. Self-reported symptoms of dyspepsia or gastro-esophageal reflux were unrelated to persistence, independent of use of H2-blocker or proton pump inhibitor medication to reduce gastric acidity.

McHorney and colleagues performed telephone surveys with 1,015 post-menopausal women identified from a pharmacy claims database as having received a new prescription for a weekly or monthly oral bisphosphonate.(41) Non-compliance, defined as a medication possession ratio from pharmacy claims of < 67%, was strongly associated with the severity of perceived side effects to the oral bisphosphonate medication, but nearly as strongly with the patient-perceived fracture reduction benefit of the medication. Concerns about the safety of medication, distinct from actually experienced side effects, were moderately associated with non-compliance.

Overall, these studies show that a substantial proportion of patients prescribed medications to reduce their risk of fractures prematurely discontinue these medications, and even among those who persist compliance tends to be suboptimal. Self-reported side effects and cost may be the most common reasons patients stop osteoporosis medication prematurely, but a significant proportion of osteoporosis medication non-persistence and sub-optimal compliance appears to be unaccounted for by these two factors. Compliance and persistence are both better among those prescribed weekly rather than daily medication to prevent fracture, and are better among those who have had a bone density test and are aware of their fracture risk. Even among these subsets of individuals, however, a significant proportion of patients do not persist with or have suboptimal compliance to osteoporosis medication, compromising the fracture reduction benefit that might be realized from use of these agents.

Consequences of non-compliance with fracture prevention medications

Several studies now have documented that among those at high risk of fracture, suboptimal compliance with prescribed fracture prevention medication is associated with a higher risk of fracture, (34, 59-65) and higher net health care utilization and costs.(60, 62, 64) The precise nature of the association between non-compliance and fracture risk, however, remains unclear. Siris and colleagues, however, could find no fracture reduction benefit for those with an MPR less than 50%, and then an exponentially greater fracture reduction benefit as MPR increased from 50% to 100%.(63) A major difficulty with these studies based entirely on administrative pharmacy and health care claims, however, is that is not clear that those with low compliance are in fact as comparable risk of fracture as those with higher compliance.

The study of Rabenda and colleagues from Belgium is helpful in that pharmacologic fracture prevention therapy in Belgium is restricted to those with osteoporosis by bone density criteria (femoral neck T-score ≤ -2.5) and/or vertebral fractures, ensuring that all of those studied are indeed at high risk of fracture. In this study, there was a linear 33% reduction in hip fracture incidence as compliance improved from an MPR of 0% to 100%.(65)

Determinants of Non-Compliance

In this section, determinants of medication non-compliance will be reviewed considering studies of medication use in general (not just for osteoporosis) in the context of the extended Health Belief Model, using principles of cognitive science, social structural symbolic interactionism, and identity control theory.

Patient medication use behavior: theoretical background

When a provider proposes to a patient that they use a medication on an ongoing basis, this represents a proposed solution to a perceived problem. The broad overarching theoretic framework behind this proposal is intended to explain how patients conceptualize threats to their health, how in particular they conceptualize one specific solution to a health threat (medication use) and why actual medication use behavior may or may not take place.

There are several key assumptions underlying this theoretical framework. First, human behavior is assumed to be goal-directed and intended to solve some problem in

that person's environment. When we view behavior as intentional, then understanding the goals of that individual and the physical and socio-cultural environment within which that person is embedded can take us a long way in our understanding of the determinants of that behavior.(66, 67) More specifically, the patient's behavior is assumed to be a function of that patient's goals, the patient's knowledge and belief structure that is germane to solving the problem, and the environmental constraints and complexity within which the patient is embedded.(66) Second, this proposal assumes that patients are seeing a physician with a goal of improving their health status *as they define it*. Hence with respect to medication use the patient has to solve three problems; first, whether or not they are at significant risk of bad health outcomes of concern to them, second, whether or not use of a medication is a reasonable way to reduce that risk, and thirdly, how to execute medication use behavior in the context of their daily task environment.

Patients potentially have a large variety of sources of information within their social network at their disposal to try to address these three issues, including family member and friends, their health care providers, patient advocacy groups such as the National Osteoporosis Foundation, a dizzying variety of internet sources and direct industry to consumer advertisements. Sorting through these sources of information can appear to be a daunting, overwhelming task to many patients. A major constraint that humans face with respect to decision making in their daily task environment are cognitive limits regarding how much information they can retain at one time, how quickly they can access that information, and how fast they can sift through and evaluate that information is their bounded rationality. (66) (67) Cognitive theorists have theorized humans will often improve their decision making efficiency through pattern recognition, whereby many individual "chunks" of information may be perceived to have stable relationships with one another, and therefore to coexist as a pattern. All of the individual "chunks" can then be recognized very quickly *in the context* of that pattern, a process called the recognition heuristic.(68) Related to this, information that has been used recently or repeatedly, is easily recognizable as part of a larger salient pattern of information, or is associated with strong emotion may come to mind quickly when searching for solution(s) to a problem, a process labeled by Tversky and Kahneman the *availability heuristic.*(69-71) Humans tend to *satisfice* rather than *optimize* in that once a satisfactory solution is found, they will often stop their search for a better or

optimal solution.(67) Implicit in this trade-off is the judgment that further search would be more costly in terms of cognitive resources and time than what might be gained by finally discovering a better solution to the problem at hand.

Heuristic paths to satisfactory decisions are often aided by *attitudes*, defined by Maio and colleagues as affective evaluation of an object or behavior, indicating some degree of favor or disfavor.(72, 73) Belief, defined as the body of facts regarding an object or behavior the individual believes to be true, is considered to be the cognitive part of an attitude, whereas *affect*, or the emotion attached to the beliefs about the object or behavior, is another facet.(74) Actual behavior is considered to be the third component of an older, tripartite conceptualization of attitude structure.(75) The affective component of attitudes sharpen their availability and strength, facilitating quick recognition of situations or objects and potentially quick allow fast decision-making and behavioral responses.

Therefore, there are several facets of a patient's medical and family history that can be postulated to be associated with medication use behavior. First, if one has had a family member that has had a serious fracture associated with osteoporosis, that may be associated with a heightened sense of one's fracture risk, especially if that family member's quality of life was substantially altered by the fracture. Similarly, a personal history of fracture may similarly be associated with a heightened sense of susceptibility, although if one recovers uneventfully from that prior fracture, the individual may have a belief that fractures do not lead to serious health consequences. On the other hand, a history of bad experiences with medications in the form of multiple adverse drug reactions may lead one to conclude that a fracture prevention medication is more likely to cause side effects, and or to conclude more quickly that an adverse health event is due to a prescription medication. Similarly, poor experience with or negative attitudes toward medications among important individuals within one's social network can potentially have a significant effect on one's own attitude toward those medications.

The cognitive and affective components of attitudes regarding health, disease states, medications, and other modalities used to treat them are generally part of a larger patterned knowledge structure, or schema. Echabe and colleagues in Spain discerned three clusters of related health and medication beliefs among 902 adults.(76)

The majority considered health to be a balance of body and mind, that illness is a break in this balance usually attributable to lack of exercise, stress, poor mood, and poverty. This subgroup believed that individuals themselves have substantial control over their own health through their own behaviors with respect to diet and stress management. In general they viewed medications negatively, believing that use of them often has negative consequences. A minority viewed illness as occasionally due to bad health habits but also due to bad luck, God, or other factors beyond one's control. This group considered physicians and use of medications as the best resources that help recovery from illness. Each of these belief structures may be very adaptive in certain contexts. Believing in their own agency with respect to their health status, those in the former group may be more likely to adopt health-conscious behaviors, and forestall the onset of one or more chronic diseases. On the other hand, once a chronic disease does begin, the potential threat to their salient, personal identities may be greater.

The relevance of all of this to health behavioral decision such as use of medications is that patients form attitudes regarding both potential health threats and possible solutions to those threats, that are then used as heuristic decision-making devices. These attitudes evolve over time in the context of the socio-cultural milieu within which individuals are embedded, as emergent phenomena from interaction with others.

Symbolic Interaction Between Patient and Provider

A major, central member of most patients' social networks with respect to their health are their health care providers, especially those with whom they have a longer and/or trusting relationship. When diagnostic screening yields evidence of a condition for which the physician recommends chronic medication therapy, the patients' vector of social and personal identities is inevitably challenged to some degree, depending on the disparity between their identity standards and the new diagnostic information about themselves that has been presented. Patients then have to arbitrage new information given to them by the provider and the *a priori* health and medication beliefs they bring to the encounter, including their perceived identity standards, their definitions of health, their conceptualizations (if any) regarding the target condition for which the physician is proposing medication, and their conceptualizations regarding medications and their use.

The relationship between a provider and a patient is imbued with many elements that may either impede or facilitate acquisition of new knowledge by the patient that is useful for the pursuit of health goals. Even though medical information is available from multiple media sources and often from other members of one's social network, there is considerable information asymmetry between provider and patient, such that the provider is in a position of relative power and the patient in a position of relative dependence.(77, 78) A perceived willingness on the part of the physician to fully disclose all relevant information regarding a medical diagnosis and proposed diagnostic and therapeutic strategies and to answer all of a patient's questions (called by some an Open Communication Style) has been repeatedly shown to be highly valued by patients, highly associated with patient satisfaction with their care, and with compliance to both recommended treatment and follow-up visits.(79-82) An ability to use elicit and understand the patient's own terminology and concepts regarding their health and to converse with the patient *in those terms* would be predicted, by principles of symbolic interactionism, to improve patients' sense that their concerns and beliefs have been understood and addressed and that the diagnostic and treatment plan that *emerges from the patient-provider interaction* incorporates or at least recognizes those concerns and beliefs.

Patients are also looking for congruence (or shared meanings) between themselves and their provider in terms of outlook and the decision making approach to their health. Congruence in terms of how decisions are made may be particularly important. Some patients clearly prefer that their physician act primarily as a knowledgeable advisor, and wish themselves to be the final arbiter of any medical decisions, but others want their physician to make all final decisions.(83, 84) A variety of studies have suggested that congruence between the patient and the physician regarding decision making style is associated with higher levels of satisfaction with care and with acquisition of self-care behaviors.(79, 80, 84-86)

Open communication and congruence in decision making may be domains of a larger construct, that of *trust in the physician*.(87, 88) This is conceptualized by Hall and colleagues to consist of trust in the physician's competence, that the physician puts the patient's interests first and is not following an agenda at odds with those interests, is honest, and will honor the patient's confidentiality.(89) Trust is necessary in a relationship in which one party is vulnerable, and the physician-patient relationship is

certainly one in which the patient has significant vulnerability with respect to dependence upon the physician to access to medical diagnostic testing and remedies, and due to the information asymmetry inherent in the physician-patient relationship.

Applications to Decisions Regarding Medication Use to Prevent Osteoporotic Fractures

Based on the theoretical concepts thus far presented, this proposal postulates that the following factors need to be present for medication use behavior to occur for management of chronic diseases such as osteoporosis. First, there needs to be a perception that the target condition poses a threat to one's health, and that reducing that threat is desirable. Second, there needs to be a perception that medication is capable of reducing that target threat, and that the benefits of that medication outweigh the perceived costs of that medication. Third, the person who concludes that medication use would be overall beneficial needs to believe that they are capable of executing that behavior in their daily lives. Finally, medication use behavior has to be incorporated into the person's daily or weekly task environment such that the person is appropriately cued to take the medication.

Perceived Susceptibility to and Severity of Osteoporosis and Osteoporotic Fracture

Nearly every theoretical model of health behavior, including the Health Belief Model (HBM) and its variants,(90-92) the Leventhal Self-Regulatory Model,(93) the Theory of Planned Behavior,(94, 95) Protection Motivation Theory,(96, 97) the Precaution Adoption Process Model all postulates perceived susceptibility to a health threat and perceived severity of that health threat as significant determinants of health behavior to reduce that threat. These constructs are modeled quite explicitly in the Health Belief Model. Subsequent variations of the Health Belief Model have included, as additional important factors influencing health-related behavior, motivation to improve health as an important factor,(98) causal beliefs of the target condition (why it is or is not a threat),(99) self-efficacy (defined as the belief one is capable of executing the behavior),(91) and locus of control.(100, 101) The HBM has been criticized for not including important cognitive factors such as social support and social norms, and for not separating out the formation of intent to carry out a behavior from the actual

execution of that behavior.(92) With respect to medication use, the model appears to emphasize the perceived benefit of the medication (or lack thereof), and barriers such as inconvenience and cost, but does not explicitly model a role for negative attitudes regarding medications in general. Many studies have used the HBM to predict medication compliance, with modest success.(90, 102, 103) These typically have operationally defined medication beliefs in terms of belief of efficacy, and barriers to use, but have not included intrinsic harm from use in these operational definitions.

Protection motivation theory and Leventhal's self-regulation theory both explicitly consider both cognitive and emotional evaluation of potential health threats. The self-regulation theory postulates that health behavior is a function of both "objective" representations of illness and of the available coping responses to the threats that illness poses, and in parallel, the emotional responses that parallel those representations.(93) Protection motivation theory and the Theory of Planned Behavior are different from the others in separating out formation of motivation or intention to perform a behavior from the actual performance of the behavior

There are many similarities and common themes in these models. Implicit in their application to use of medications to prevent osteoporotic fracture or diabetic complications is the concept that individuals first judge whether or not the condition does or does not indicate a threat to their health, whether or not protection of their health is worthwhile relative to other demands in their task environment (and therefore, whether or not the health threat constitutes a "problem to be solved"), and finally whether or not medication use represents a desirable response to the problem.

Most investigations of health behavior to reduce the risk of osteoporosis have focused on use of non-medicinal preventive behaviors such as ensuring adequate calcium intake, vitamin D intake, and increasing the frequency of weight-bearing exercise, using the Health Belief Model or one of its extensions, the Theory of Planned Behavior, or the Weinstein Precaution Process Adoption Model as their conceptual framework. Most of these studies show an association between perceived susceptibility to osteoporosis and either intention to improve calcium intake or actual increased calcium intake.(104-108) Perceived severity generally has been operationally defined as feelings of being frightened by or dread at the idea of having osteoporosis, or agreeing with a statement that osteoporosis is a serious disease. Generally, these

studies have not shown that perceived severity is associated with intention to increase or actually increased calcium intake. One study has specifically investigated determinants of intention to increase vitamin D intake, and in that study perceived susceptibility to fracture was associated with both a heightened intention to increase and subsequent use of vitamin D supplements.(109)

Having a bone density test showing low bone mass and therefore a *personal* increased risk of fracture is associated with a higher utilization of medication to reduce fracture risk, especially for those who are knowledgeable about their bone density results.(110-113) Whether those with very low bone density and therefore at high risk of fracture who choose not to start drug therapy still did not perceive a susceptibility to fracture or chose not to do so for other reasons was not clear in these studies.

Disease knowledge.

Knowledge of the threat that a target condition may pose is an important component of perceived susceptibility to and seriousness of that target condition, according the to the theoretical frameworks of the Health Belief Model and its various extensions,(90, 92, 100, 101) Protection Motivation Theory,(96, 97) and the Precaution Adoption Process Model.(114, 115) However, applications of these formulations of knowledge have not always made clear the conceptual difference between *belief* and *knowledge*. For the purposes of this project, I am defining *osteoporosis knowledge* as that body of facts for which there is broad consensus within the allopathic medical community that they are true. *Beliefs* were previously defined as what an individual or community of individuals cognitively considers to be true – and hence osteoporosis knowledge as defined above still is a set of beliefs. Nonetheless, I am defining osteoporosis knowledge as above to clearly distinguish it from beliefs of patients, which generally overlap but are not fully congruent with osteoporosis knowledge as I have defined it. Almost all of the published empirical studies of patient knowledge about osteoporosis have taken this same approach, using *criterion* tests to assess knowledge whereby answers to either multiple choice or (more commonly) true-false questions are judged to be right or wrong.(116)

Osteoporosis knowledge can be sub-categorized as knowledge about risk factors and epidemiology, non-pharmacologic preventive measures, association with and consequences of fractures, and available treatment. The majority of osteoporosis

knowledge measures have tested knowledge regarding risk factors and preventive measures (e.g., calcium supplementation and weight-bearing exercise), among convenience samples of healthy adults or else samples of college-age, middle-aged, or older adults who may at risk for but have not specifically already been diagnosed with osteoporosis.(117-128) Fewer studies have included items in their instruments to assess knowledge of the association of osteoporosis with fractures, (120, 129-133) or of the consequences of those fractures.(131, 132) Only two have assessed knowledge of the availability and effectiveness of pharmacologic treatment to prevent fracture.(133, 134) Generally, these studies have shown that knowledge regarding risk factors for osteoporosis and preventive measures to be fair to moderately good, but to be poor for knowledge regarding consequences of fractures. Most, but not all, studies have found knowledge regarding osteoporosis risk factors and preventive measures to be associated with preventive behaviors.

Importantly, no studies to date have assessed the association of knowledge regarding the association between osteoporosis and fractures and the health consequences of those fractures and medication use behavior. Arguably, among those *already diagnosed with osteoporosis*, knowledge of fracture risk, health consequences of fractures, and availability of effective treatment is much more relevant for decision making regarding use of medications than knowledge of risk factors for osteoporosis per se.

For those already diagnosed with osteoporosis, general knowledge regarding osteoporotic fractures may be only moderately associated with perceived susceptibility to those fractures, for a variety of reasons. They may not have accepted the diagnosis of osteoporosis, or else feel that they are to some degree exempt from the risk of fractures for a variety of reasons. They may believe that if they have already had a fall or two and did not break any bones that their bone strength is adequate. They may believe that if family members or others with whom they closely identify themselves had osteoporosis but did not fracture, that they too are at least somewhat exempt from risk of fractures in spite of the diagnosis of osteoporosis. They may believe that they can avoid falls, or that *because* of their use of calcium supplements, weight-bearing exercise, and/or medications they are at lower risk. The tendency to invoke self-exemption from harm has been documented in some hypertensive patients who believe that they (but not others) can tell if their blood pressure is elevated and

therefore that it is safe to use their anti-hypertensive medications as needed, rather than on a regularly scheduled basis. Smokers have also been shown to have a tendency to believe that they are exempt from the adverse health effects of smoking. Whether or not self-exemption beliefs are employed by patients with osteoporosis to minimize their perceived risk of fracture is unknown.

On the other hand, experience with friends or close family members who have suffered from osteoporotic fractures may increase one's sense of susceptibility even without detailed knowledge of the disease. Therefore, while nearly every social cognition model of health behavior predicts that disease knowledge would be associated with perceived susceptibility to the adverse consequences of the target condition, disease knowledge is likely to be neither a necessary nor sufficient condition for a person to feel susceptible to that target condition. Nonetheless, effective communication and education regarding the target condition and its adverse health consequences is one of the main tools health care providers have available to encourage compliance to medication that reasonably can be expected to improve health outcomes.

Medication Perceptions

Several studies that utilized focus groups to gain insights into how patients conceptualize medications are summarized in table 1 on page 15. While these studies were done in patient samples with different medical condition, certain common themes emerge. First, as has been identified in many of the health behavior models previously discussed, is that patients look to somatic feedback to inform them if medication is truly necessary. This is problematic especially for proposed medications to prevent future adverse health events for patients who currently are asymptomatic. Several studies have shown that trust in the provider and adequate communication of a rationale that is consistent with the patient's lay beliefs for medication use in the absence of symptoms is necessary for compliance.(85)

Unson and colleagues interviewed post-menopausal women in the context of six focus groups.(135) As predicted by the health behavior models previously discussed, willingness to take or consider taking medication to prevent osteoporotic fracture was often expressed contemporaneously with concern regarding the risk of and morbidity due to fractures, and faith in the efficacy of reducing those

risks. Skepticism regarding medication to reduce osteoporotic fracture was associated with doubts regarding the physician's assessment of their fracture risk or knowledge of the proposed medication. Concerns were also raised regarding unknown risk of harm especially with long-term use, and lack of understanding of how they actually work to reduce fracture risk. Discomfort with medication use was also associated with a view that they are "unnatural substances".

Britten's interviews with 30 general practice patients (not selected for diagnosis) in the United kingdom, revealed similar themes regarding medication representations.(136) Self-reported compliance was associated with trust in both physicians and in the intrinsic safety of medications. Self-reported non-compliance was associated with substantial concerns regarding safety with long-term use (especially regarding possible carcinogenicity), discomfort with use of medications as "unnatural substances" (one participant described medications as "an alien force"), and fears about either having one's health status being too dependent upon medication. This study also revealed a sense of shame at having to take medication among some participants, suggesting that an unfavorable social identity is associated with medication use for some.

Conrad's interviews of patients with epilepsy reveal how difficult these conflicting feelings can be for patients with conditions that truly require intervention for adequate social functioning.(137) Use of medication in this instance for many patients is viewed as a "ticket to normality". On the other hand, these patients also struggled with the sense of being dependent on them, and would often alter their dosages according to their perceived need in part to exert some control over the medication regimen. They also expressed fears about their social identity being defined in part by their disease label and need for medication.

The study of Adams and colleagues of asthma patients revealed that medication use can be resisted if in the mind of the patient this requires accepting a disease label that is strongly undesirable.(138) Those patients that refused to take inhaler medication on a regular basis to prevent asthma attacks viewed the label "asthmatic" as being associated with being weak, and socially ineffective and unattractive. These patients went to some lengths to hide their condition from others. Fears were also expressed about being too dependent upon medication to maintain a

sense of good health, and that daily use of medication involved ceding some control over their health status to the medication.

Table 1-1: Facets of Negative General Medication Beliefs

Study / Citation/ Diagnoses	Fear / Concern						
	Direct Harm*	Dependence	Loss of Social Identity	Loss of Control over Health Management	Artificiality of Meds	Lack of Understanding How They Work	Physician Overuse or Misuse of Medication
Unson, et. al., 2003, Osteoporosis	X				X	X	X
Britten, 1994, General Practice	X	X	X		X		
Conrad, 1985, Epilepsy		X	X	X			
Adams, et. al., 1997, Asthma		X	X				
Lin, et. al., 2003, Depression	X	X	X		X		X
Donovan, 1992 Rheumatoid Arthritis		X		X	X	X	
Benson & Britten, 2002, Hypertension	X	X	X		X		X
Horne et. al., 1999, Renal Failure or MI	X	X		X	X	X	X

*Especially with long-term or continuous use

Among patients with rheumatoid arthritis, concerns regarding the artificiality of medications, loss of control over management of one's health status, and risks of harm are also common.(77) These patients also expressed concern over being too dependent upon their medication. Compliance was associated with more detailed understanding regarding how the medications actually work to improve their health status and how they would be monitored to ensure their safety.

More recently, Benson and Britten have conducted interviews with 38 patients with hypertension from two general practices in the U.K. While these patients did not directly indicate concerns regarding ceding control of their health status to medication, they did nonetheless express a concern regarding becoming dependent on

medication[1], thus compromising their social identity. These patients also expressed fears of long-term harm from medication, and concern that physicians excessively recommend medications for medical problems.

Finally, Horne and colleagues conducted their own qualitative interviews of 35 patients who either had suffered a recent myocardial infarction or were on chronic hemodialysis. All of the themes noted above, save one, were expressed by some of these patients, including fears of unknown risks from medications, being dependent upon them, physicians being too eager to prescribe them, lack of understanding of how they work to reduce the threat of the target condition, the artificiality of medications, and the sense of loss of control over their health management when using medication according to a set prescribed schedule. Compromised social identity was not specifically identified as a concern among these patients, although it is possible that concerns regarding becoming dependent upon medications and ceding control of one's health status to medications for some people are related to their vector of social identities.

In summary, these qualitative studies do confirm the importance of the constructs of perceived threat from the target condition and self-efficacy in executing medication use in one's daily life. They also, however, highlight the potential importance of negative beliefs and representations regarding medications for medication compliance.

Measurement of Beliefs Regarding Medication Necessity and Concerns

Four measurement instruments regarding medication beliefs and attitudes have been constructed, for which some psychometric testing has been done. The *Health Belief Indices* were constructed by Jette and colleagues to specifically operationalize for measurement the constructs of the Health Belief Model.(139). The domain specifically pertaining to medication attitudes, Perceived barriers to Taking Medications, consisted of four items asking respondents how likely they would stop taking medication recommended by their physician under four conditions; the

[1]Dependence in all of these interviews does not really refer to addiction per se, although participants in many of these studies also expressed fear of that as well. While none of the authors of these studies explicitly define what they mean by dependence, from the transcribed comments of many patients, it appears to define a sense that one cannot function or carry out one's social roles without them, and also a tendency to look to medication too readily as a solution to problems. It seems, therefore, probable that fears of dependency might be correlated with fears of compromised social identity.

medication cost a lot, they felt worse when taking it, use of the medication was hard to fit into their daily routine, or if they had read the use of the medication might be dangerous. Lin and colleagues have developed a 12-item disease-specific instrument to assess attitudes regarding anti-depressant medication.(140) This scale includes items that assess the degree to which respondents feel that medications are overused, represent a “crutch” that individuals should be able to do without, and should not be taken long-term. The scale includes items regarding attitudes toward anti-depressant medication compared to non-medicinal approaches such as exercise and nutrition, and also regarding the effectiveness of medication in preventing depression relapse.

McDonald-Miszczak and colleagues have developed a survey instrument consisting of three domains designed to assess constructs postulated to be important to medication compliance.(141) These three constructs are ability to deal with health professionals (who are prescribing their medications), confidence in one’s memory to remember to take medication, and attitudes regarding medication. The authors were primarily concerned with self-assessed efficacy in each of these areas, and hence the scale for the medication attitude domain assesses primarily self-assessed confidence that the medication will be efficacious, that the dosage is correct, and the appropriateness of the medication for their condition (appendix 2). This domain does also includes items regarding side-effect experiences, nervousness about taking medication for a long period of time, fear of side effects, and concern regarding complexity of the medication regimen.

The best developed general survey instrument regarding medication perceptions is the *Beliefs About Medications Questionnaire (BMQ)* developed by Horne and colleagues from an pool of 34 items, comprising statements regarding the necessity of medication that specifically had been prescribed, concerns regarding those same medications, general concerns regarding overuse of medications and excessive prescription of them by physicians, and concerns regarding general harm from medications.(142) These items were constructed based on the qualitative focus group studies reviewed in previous section of this paper, including the focus groups of a total 35 patients who had had a myocardial infarction or who were on hemodialysis that Horne’s research team themselves interviewed. These items were then administered to 120 patients with cardiac disease, and exploratory principal components analysis carried out. Exploratory factor analyses revealed four separate

factors, two regarding medications respondents had personally been prescribed by their physicians, and two regarding medication in general. The two specific factors were Specific Necessity (how necessary they viewed use of their medication so to be to maintain their health status), and Specific Concerns (how concerned they were about potential harm that may accrue from use of their current specific medicines). The two general factors were labeled General Overuse (assessing respondents belief that medications are overprescribed by physicians and overused by patients), and General Harms (assessing respondents beliefs that medications are inherently dangerous or unsafe).

The Specific Concerns scale appeared to have been most consistently reliable, with Cronbach's alpha ranging from 0.63 in psychiatric patients to 0.80 in diabetic patients. The Specific Necessity scale had good internal consistency reliability (Cronbach's alpha 0.74 or higher) with the exception of hemodialysis patients, for whom Cronbach's alpha was only 0.55. The General Overuse scale also showed good internal consistency reliability in all groups except one, with Cronbach's alpha being 0.60 among General Medicine poor internal consistency reliability in three of the six groups (Cronbach's alpha values of 0.47, 0.51, and 0.51 in asthmatic, cardiac, and general medicine patients respectively). No one item appeared to be responsible for any of the suboptimal results in any of the subgroups.

Horne and colleagues have subsequently demonstrated nomological validity of the Specific Necessity and Concerns subscales in the cardiac, hemodialysis, and asthma subsets, as well as an additional cohort of oncology patients.(143) A Necessity-Concerns difference score was calculated by subtracting the raw Concerns score from the raw Necessity score. The Specific Necessity scale scores correlated with self-reported compliance rank in all groups except the hemodialysis patients. The Specific Concerns and the Necessity-Concerns differential appeared to be highly correlated in all four groups.[2]

In more recent years, perceived necessity for medication and medication concerns have also been shown to be associated with compliance with daily inhaled glucocorticoid medication to control asthma,(144, 145) and with anti-retroviral therapy among patients with acquired immune deficiency syndrome (AIDS).(146, 147) For

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This statistical analysis may be invalid, however. They acknowledge that their self-reported adherence is ordinal, and explicitly use self-reported adherence rank, yet reported Pearson correlation coefficients rather than using the non-parametric Spearman correlation test.

those with asthma, perceived necessity explained 15.8% of the variance of self-reported compliance with glucocorticoid inhaler use.(144)

Presumably, perceived necessity of medication to treat a target condition would be present only if patients perceived that they were susceptible to the adverse consequences of that target condition, and that those consequences were sufficiently serious to warrant action on their part to lower their risk. On the other hand, perceived susceptibility to significant adverse consequences of a target condition might not lead to perceived necessity for medication if that person perceived that there were adequate non-medicinal ways to lower their risk. In this way, perceived susceptibility may be a necessary but insufficient condition for medication to be perceived necessary to reduce one's risk of adverse health events related to a target condition.

Barriers to Utilization of Medication

Costs

Financial out of pocket cost of medication is well documented to be one of the most important barriers to their prescribed use, at least among low-income populations. Cross-sectional studies have generally shown an association between extent of prescription drug coverage and utilization of medication to treat hypertension,(148, 149) diabetes mellitus,(150, 151) cardiovascular disease,(152) reactive airways disease,(153) hyperlipidemia,(151, 152, 154) and depression,(151) but not necessarily among those with epilepsy,(151) congestive heart failure,(151) or following a myocardial infarction.(155) Longitudinal quasi-experimental studies following cohorts of patients through changes in their out of pocket medication cost burden have generally found that elimination of coverage(151, 156, 157) or moderate to high increases in copay or co-insurance(158-164) have been associated with reduced utilization of medication. Surveys of several cohorts have shown that 7 to 20% have self-reported discontinuation or reduction of their medications due to cost, with cost-related medication reductions more likely among women, those with low income, higher out of pocket monthly drug cost burden, and minority populations.(165-173) Providing medications free of charge following renal transplantation,(174) those with diabetes mellitus,(175) and indigent patients with heart disease(176) significantly improved, but did not eliminate, non-compliance.

Drug cost burden, especially among low-income patients, has been shown to be associated with increased nursing home admissions among the elderly(177) and in some studies with an increased risk of hospitalization,(178) confirming that it is an important predictor of medication non-compliance. Nonetheless, a substantial proportion of non-compliance may not be explainable by drug cost burden. First, even when medications are free of charge or available at minimal out of pocket cost, persistence with anti-rejection drugs among renal transplant recipients(174) and with statin drugs among those with hyperlipidemia(26) have been as low as 50% at one year. Second, even among patients with significant co-pay or co-insurance, cost burden may not be the dominant concern patients have about being on chronic medications.(179) Third, some patients choose to cut back on other expenses rather than their medications even when their out of pocket medication costs are significant.(167, 171) Fourth, when patients do cut back medications on account of cost, by self-report they are selective regarding which ones they do cut back, also considering their perception of the threat the target condition(s) pose to their health, and the perceived effectiveness of each medication.(169) Finally, patient's may be more likely to comply with medications in spite of some perceived medication cost burden if they have substantial trust in the prescribing physician.(180) These studies suggest that the *interaction* of medication beliefs with drug cost burden may be a significant predictor of medication persistence and compliance.

Regimen complexity

Regimen complexity has generally been operationally defined simply as the number of medication doses per day.(181) Almost without exception, compliance appears to decrease as the number of doses per day increases.(181-187) In other words, compliance with once daily regimens are better that twice daily regimens, which in turn appear to be easier to adhere to than three times daily regimens, and so on.

Given that so many patients, especially among the elderly, are also on multiple medications, regimen complexity could conceivably also be defined as the number of medications per day, or as the product of daily doses and daily medications. The association of the number of prescribed medications with compliance is much less clear, however, with studies either showing a negative association,(188) a positive association,(37) or no association(189, 190) between the number of prescribed

medications and medication compliance. On the other hand, when two medications are prescribed for the same condition, compliance to a fixed combination of the two in one tablet or capsule may be better than compliance to the medications given separately.(191) Among patients with acquired immune deficiency syndromes, an additional dimension of regimen complexity is the need to time medication with food or the absence of food, and this has also been associated with reduced medication compliance.(186, 187, 192)

Specifically among those with osteoporosis, compliance with once weekly bisphosphonates is better than with once daily bisphosphonates.(31, 38) Additionally, compliance with once monthly ibandronate (just released on the market in 2006) may be better than once weekly alendronate.(193)

Social Support

Several other factors may play either impede or facilitate medication compliance. *Social support* has been in general associated with better health status,(194, 195) and DiMatteo has postulated that compliance to medical treatment regimens may be an important mediating factors between social support and health status.(196) Emotional and informational social support have been shown to be of importance in compliance to a wide variety of health behaviors, including keeping physician appointments, maintaining dietary compliance, use of insulin blood glucose testing among those with diabetes mellitus, and medication compliance.(196, 197) Instrumental social support, that is actions on the part of others that directly facilitate one's medication use behavior (such as putting medications out or giving reminders to take the medication) has been most consistently and strongly associated with compliance.(196) This may be particularly important to sustain compliance among cognitively impaired or frail elderly.(198, 199) Structural social support, operationally defined as living with someone or being married, is positively associated with compliance to medical treatment, as are measures of family cohesiveness.(196)

Few studies have assessed the association of social support with medication compliance exclusive of compliance to other behaviors such as keeping provider appointments. Most of these have found a positive association between compliance and social support, but in general have modeled social support as a unidimensional

concept without attempting to distinguish emotional, informational, instrumental, and structural aspects.(200-205)

Medication use self-efficacy

Self-efficacy, defined as the belief that one is capable of action that can result in favorable outcomes, in general has been linked to better health status.(206) Self-efficacy is linked to a sense of personal behavioral control, more optimistic outcome expectancies, higher motivation to act, and greater effort to achieve the target behavior/outcome. Self-efficacy has in particular been studied with respect to health behaviors such as diabetes self-care,(207, 208) avoidance of addictive substances, dietary compliance, and avoidance of risky sexual behavior.(206) With respect to medication compliance, higher self-efficacy with respect to compliance to complicated medication regimens to treat acquired immune deficiency has been associated with subsequent actual compliance to the regimen.(186) Among those with osteoporosis, medication use self-efficacy has been associated with self-reported compliance with medications to reduce risk of fracture.(209)

Other Barriers/Facilitators of Medication Compliance

Poor memory or cognitive impairment,(210-215) and regimen complexity,(181, 213, 216-219) have been shown to be associated with non-compliance. Even modest impairment of executive cognitive function among the elderly has been shown to be associated not only with significant difficulty executing appropriate medication use behavior, but also with a lack of recognition of that difficulty.(77) Only a couple(220, 221) of several studies(212, 222-224) have found competing demands from co-morbid medical conditions to adversely affect medication compliance, independent of the number of prescribed medications and regimen complexity. Depression, however, is the one co-morbid condition that consistently has been shown to adversely affect medication compliance in those with diabetes mellitus,(225-229) and other chronic disorders.(173, 230)

Demographic factors such as age, marital status, and education level have been generally been found to be either unrelated to medication compliance or to explain only a very small proportion of the phenomenon.(154) Many studies within the United States have found lower rates of compliance among African-Americans than Caucasians,(26, 154, 231, 232) but others have not.(183, 233, 234)

Gaps in Current Knowledge

There are several important gaps in our current base of knowledge regarding the relationship between attitudes regarding medications and medication compliance. First, it is not clear how strong the relationship is between medication attitudes and compliance, relative to other variables such as the relationship with the prescribing physician, drug costs, and medication regimen complexity. Moreover, even if medication beliefs are only weakly associated with compliance relative to other predictors such as side effects, drug costs, and perceived target condition threat, interactions between medication beliefs and these variables may be important predictors of compliance. Second, while trust in one's physician is associated with self-reported compliance,(79, 85) the degree to which trust in the prescribing physician influences medication compliance independent of medication attitudes (or in spite of negative medication attitudes) is unclear. In other words, will patients adhere to medication in spite of negative concerns regarding them if it is recommended by a physician in whom they have a substantial degree of trust? On the other hand, perhaps trusted physicians improve their patients' medication compliance specifically by altering their patients' medication attitudes, in which case one would expect any association between the patient-provider relationship quality and medication use behavior to be mediated by these variables.

Third, the relationships between medication beliefs, knowledge regarding the health consequences of fractures, objective indicators of actual fracture risk, and compliance with fracture prevention medication is unknown. For example, if those whose medication attitudes are such that they choose to be non-compliance are also less informed regarding the risks and consequences of the diseases the medications are intended to treat and/or have attitudes regarding their fracture risks and fracture prevention medications that not are not realistic, then better targeted education regarding those risks and consequences may still be fruitful. On the other hand, if those who are non-adherent with medication appear to understand overall the risks of and consequences of the diseases those medications are designed to ameliorate, then medication non-compliance in that situation can justifiably be considered to represent informed decisions.(77, 235) Moreover, one can have accurate knowledge in general regarding asymptomatic conditions such as hypertension, and still believe that one's own risk for complications of those conditions are low. For example, Meyer and

colleagues documented instances of nurses quite knowledgeable that symptoms do not accurately reflect blood pressure who nonetheless thought that they could tell when their blood pressure was elevated (that they were, in essence, an “exception to the rule”).(236) The degree to which disease knowledge and beliefs regarding personal susceptibility are discrepant bears further investigation.

Fourth, predictors of medication non-persistence due to side effects may differ from non-persistence for reasons other than side effects, and both of these sets of predictors may be different from predictors of compliance among those who still have a current oral bisphosphonate prescription. Studies to date have conceptualized side effects as a cause of non-persistence per se. However, a “side effect” requires both the occurrence of an adverse event and a causal attribution of that event to the drug in question. Those with prior bad experiences with medications and/or concerns about the long-term safety of medications may be much quicker to attribute adverse events to a prescription drug.

The definition of non-persistence itself implies that this is a product of a deliberate decision-making process. Among those who have not deliberately stopped their medication, non-compliance can be either intentional or non-intentional.(211, 237) Hence, further investigations regarding the similarity and differences of predictors with these different aspects of medication use behavior may shed further light on how patients make decisions about their medication use, and guide strategies to encourage appropriate use of medications to reduce adverse health events.

Specific Aims

The principal aims of this cross-sectional retrospective study of a cohort of individuals diagnosed with osteoporosis are as follows.

1. Estimate the association between perceived necessity of fracture prevention medication and self-reported persistence due to side effect, self-reported persistence for reasons other than side effects, and self-reported non-compliance with oral bisphosphonate therapy.
2. Estimate the association between concerns about the long-term safety of and dependence upon medications in general and self-reported persistence due to side

effect, self-reported persistence for reasons other than side effects, and self-reported non-compliance with oral bisphosphonate therapy.

The secondary aims are as follows;

1. Estimate the association between medication use self-efficacy and self-reported persistence due to side effect, self-reported persistence for reasons other than side effects, and self-reported non-compliance with oral bisphosphonate therapy.
2. Estimate the association between objective indicators of fracture risk (bone mineral density, prevalent vertebral fracture on lateral spine imaging, personal history of fracture, and family history of fracture) and self-reported oral bisphosphonate non-persistence and non-compliance.
3. Estimate the association between objective indicators of fracture risk (bone mineral density, prevalent vertebral fracture on lateral spine imaging, personal history of fracture, and family history of fracture) and perceived necessity of fracture prevention medication.
4. Estimate the direct association of the patient –provider relationship quality with self-reported fracture prevention non-persistence, and the indirect association mediated through perceived need for fracture prevention medication, concerns about medications, and medication use self-efficacy.

Chapter 2: Research Methods, Survey Results, and Latent Variable Factor Analysis

This chapter is intended to explain the structure of the survey instrument used in this project and to present a principal components analysis of the survey items intended to measure latent variables in the model. The variables assessed by medical record review will be explained in the context of the three papers to follow.

Conceptual Framework

The conceptual framework for this research proposal (**figure 2-1**) is based in part on an expanded version of a expectancy-value model of individual health behavior, the Extended Health Belief Model.(94, 95) Patients use of a medication is postulated to be strongly influenced their perceptions of the benefits and costs (both financial and non-financial) of taking that medication. Focus group research studies of patients with a variety of chronic diseases have shown that patients themselves tend to conceptualize their actual use of medication as *necessary* to achieve one or more health goals. In this study, the perceived net health benefits of medication use are operationally defined as the perceived necessity of medication for the target condition. The perceived necessity of medication is postulated to be driven in part by the interaction of two variables; their perception that they are *susceptible* to the target condition and the *perceived severity* of the target condition should it occur. Each of these is considered by themselves to be necessary but insufficient for an individual to perceive that a medication is necessary for their health, and hence the model postulates that the interaction between these two rather than their main effects, will be associated with the necessity for fracture prevention medication.

Other expostulations of the Health Belief Model postulate perceived effectiveness of the medication to treat the target condition as a predictor of medication use behavior. This is incorporated in the perceived necessity of fracture prevention medication in the model for this current project, and does not appear to be a separate construct, as will be demonstrated in the factor analysis that follows toward the end of this chapter. Usual representations of the Health Belief Model differ from the variation used in this project in that perceived benefits, barriers, and costs are postulated to be directly associated with health behavior, without the mediating variable of perceived necessity.

Perceived necessity for medication is also influenced by concerns about the long-term safety of and dependence upon medications. Concerns about medications are often generalized, in that individuals often think of all medications as having some general negative qualities. Given that perceived need for fracture prevention medication includes the belief that use of a medication is necessary to maintain or improve one's health, concerns about the long-term harm of medications logically will have a negative association with those beliefs.

Concerns about medication are also postulated to have a direct effect on medication use behavior for two reasons. First, this construct also includes the sense of dependence upon medications and the implicit negative effect of that dependence upon one's overall sense of control over one's health status and vector of social identities. These may not be considered to affect the necessity of medications per se, but nonetheless be a motivator not to use medication to address a particular health problem. Second, given that these constructs are latent variables and that our measurement of them are imperfect, there may be a portion of the effect of concerns on medication necessity that is not captured, that nonetheless appears as a direct effect on medication use behavior when the model is estimated

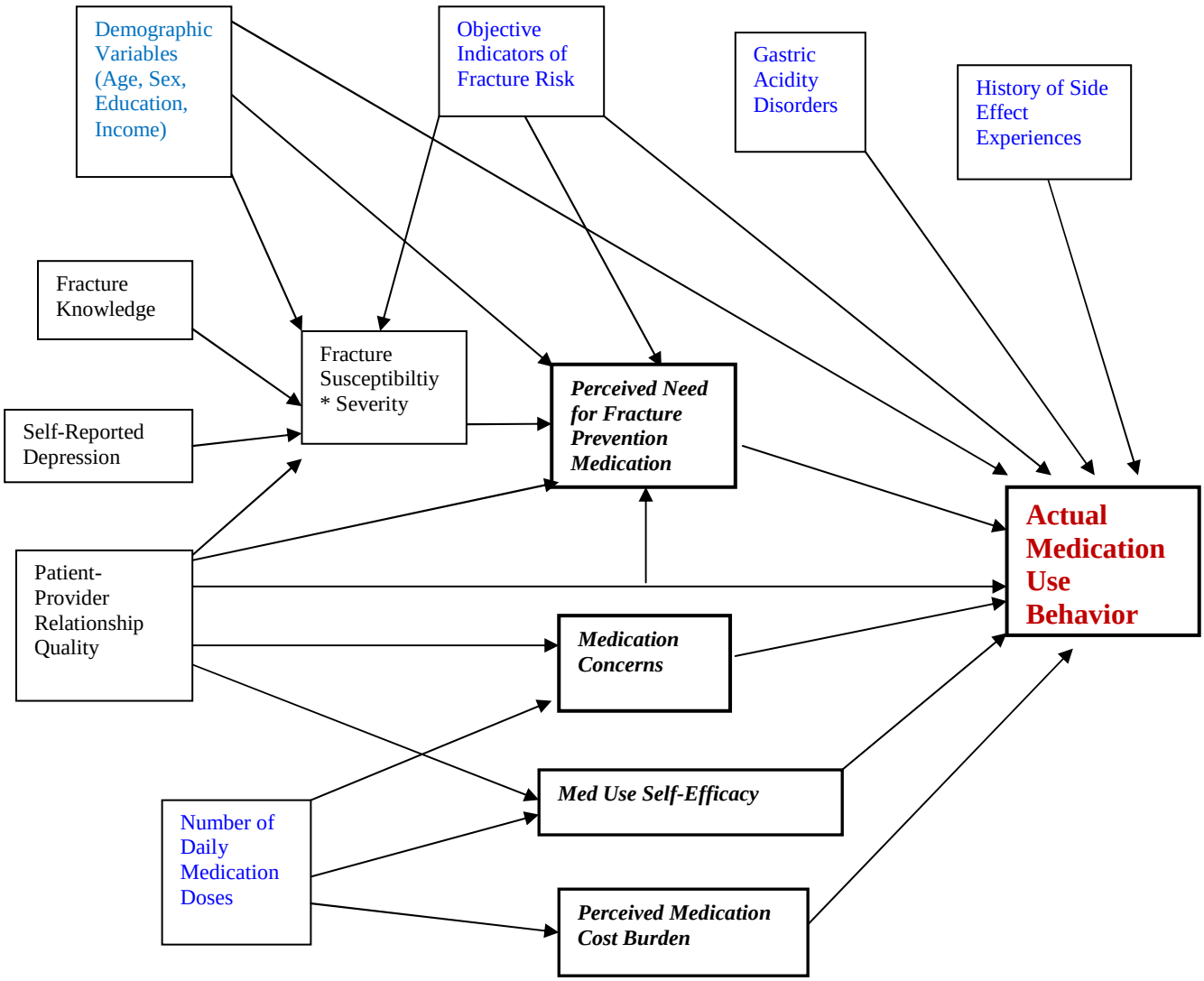
Medication use behavior will, of course be influenced by the direct experience of side effects. Generally studies of medication compliance treat "side effects" as an independent predictor of medication use behavior. The experience of side effects themselves, however, requires both the occurrence of an adverse event and the causal attribution of that event to one or more medications. However, individuals may vary significantly in their proclivity to conclude that an adverse event is due to one or more of their medications. In this study, non-persistence with fracture prevention medication was conceptualized as non-persistence due to side effects, non-persistence for reasons other than side effects, and non-persistence for any reason. Experience of and perceived severity of side effects was not directly assessed. The most common side effect from oral bisphosphonate medication to prevent osteoporotic fractures is stomach upset, and a history of or current gastric acidity disorder is therefore postulated to have a direct effect on medication use behavior. Prior adverse drug reactions, indicative of personal bad experiences with medications, may logically strengthen an individual's proclivity to attribute an adverse event to one or more of their medications, and hence the number of medications to which a person has had adverse

events is postulated to be a predictor of medication use behavior, especially non-persistence due to side effects.

Perceived susceptibility to and severity (health consequences) of fractures are postulated to be driven by both personal and family history of fractures. Similarly, low bone mineral density and prevalent vertebral fractures are postulated to affect an individual's perceived susceptibility to and severity of fractures. General knowledge of the high prevalence of osteoporosis and the health consequences of fractures is also perceived to influence perceived personal susceptibility to and severity of fractures. At first glance, it appears that knowledge of the health consequences of fractures and perceived susceptibility to fractures would be part of the same construct. However, the knowledge questions are general (such as "do hip fractures permanently affect a person's ability to walk?") whereas the fracture susceptibility questions are specific for that person ("a hip fracture would have serious permanent consequences for my health"). An individual can believe that hip fractures are in general associated with serious health consequences, but that one would be relatively except from those consequences should a fracture occur on account overall health, how well one takes care of oneself, or genetic constitution.

Patients' perceptions of their relationship with their physician are postulated to influence their medication use behavior in three ways. First, physicians potentially have substantial influence over the level of knowledge that patients have about the target condition and the adverse health consequences of that condition as well as about the medications themselves. Physicians are also postulated to have substantial influence over the degree to which patients view their susceptibility to the consequences of the target condition, how severe they believe those consequences would be for themselves personally, and patient beliefs in the efficacy of the proposed medication. Their acceptance of and belief in the advice and education that they receive regarding the threat to their health from the target condition and the risks and benefits of the proposed medication to reduce that threat will be influenced by their trust that the physician is competent and knowledgeable about osteoporotic fractures, is truly is concerned about their welfare, involves them in the decision-making process regarding management of their health status, and openly communicates the information perceived by the patient to be necessary to make an informed choice regarding use of the proposed medication.

Figure 2-1: Conceptual Model of Medication Use Behavior in Osteoporosis (Medication Attitude Variables in Black, Others in Blue)



*Not shown; direct effects of demographic variables on medication concerns, medication use self-efficacy, and perceived medication cost burden

Medication use behavior will also be influenced by other facilitating or inhibiting factors, such as sense of self-efficacy in medication use, perceived medication cost burden, perceived instrumental social support, and medication regimen complexity. Generally, co-morbidity has not been shown to be associated with medication use behavior, with the exception of depression. and depressed mood. Finally, experience of actual medication use will influence both medication perceptions (such as through the direct experience of side effects).

Operational Definitions of Concepts for Measurement

The latent variables in the model were assessed by a mailed survey. The items used in the survey (**Appendix A**) were pre-tested by Dr. Schousboe with the assistance of Elizabeth Kind, RN, a survey researcher at Park Nicollet Institute. The pre-test consisted of going over the survey individually with five patients to be sure that all questions were clear and being interpreted by these respondents as intended.

Medication Persistence and Compliance

The primary dependent variables in this cross-sectional study will be self-reported medication persistence and compliance (**Table 2-1 and Appendix A**). *Persistence* is defined as not going more than one entire month without medication, whereas *compliance* is defined as an ordinal variable; missing none, or 1, 2, or 3 doses of medication for osteoporosis the prior month. This self-report compliance measure is based on the regimen screen of the Brief Medication Questionnaire, developed by Svarstad and colleagues.(238) The overall persistence score will be a dichotomous variable, as either persisting with medication or not persisting either for side effects or other reasons to suit their needs. Similarly, overall compliance score will be the sum of number of times in the past month that medication for osteoporosis has been forgotten or foregone for other reasons.

Patients by and large over-report their compliance to medications, and hence the sensitivity of self-report for non-compliance established by refill records, pill counts, or pharmacy refill records in general is suboptimal,(238-243) and self-reported compliance correlates poorly to moderately with other methods such as pill counts, pharmacy refill records, and electronic pill cap monitoring.(244-246) However, the accuracy of self-report relative to other methods such as pill counts and electronic pill

cap monitoring can be improved by using diaries or questionnaires as opposed to interviews (either via telephone or face-to-face), using non-judgmental language that does not connote a social expectation of compliance such that the incentive to over-report for reasons of social desirability is lessened.(245) Second, self-report compliance measures that ask respondents to estimate their use of medication over a recent brief period of time (e.g., over the most recent week) may be more accurate than measures that attempt to assess compliance over a longer time span.(247, 248) Svarstad and colleagues devised the Brief Medication Questionnaire, which asks patients to write in a list the medications they have used over the past seven days, how many days they took each medication, how many times a day they took it, how many tablets they took for each dose, and how many doses they had missed or skipped. In a small cohort of 20 patients treated with 3 or more medications for hypertension or heart failure, this measure was 80% sensitive and 100% specific for non-compliance, defined as consumption of less than 80% of prescribed doses as determined with electronic pill cap monitoring.(238) In another cohort of 236 patients who had been on a medication for hypertension for at least six months, those who self-reported missing two or more doses during the past week had estimated compliance by electronic pill cap monitoring of 61% over a three month period (interquartile range 47%-85%), those who self-reported missing one dose had an estimated compliance of 90% (interquartile range 81%-100%), and those who self-reported missing no doses had an estimated compliance of 99% (interquartile range 90% to 109%).(247) The participants in this study were highly educated and were more likely than average to adherent (since they had to have evidence of anti-hypertensive use for six months to qualify for the study) and hence whether or not this self-report measure would be as accurate in other populations is unknown.

As a validity check on the self-report persistence measure, documentation of stopping a fracture prevention medication and not prescribing the same or a different fracture prevention medication for more than one month after that stop date was sought from review of the electronic medical record, and the agreement between overall self-reported non-persistence and medical record non-persistence will be assessed by the kappa statistic. Similarly, we will have available pharmacy claims for a small subset of the study population that uses HealthPartners insurance for their pharmacy benefits. From these records, the Medication Possession Ratio (MPR) was

calculated, which is the number of tablets dispensed between the first and last fills divided by the number of tablets the patient would have obtained under the assumption of 100% compliance.(241, 249, 250) Non-compliance was defined as an MPR < 0.80, and the agreement between non-compliance from pharmacy claims and self-reported non-compliance (defined as a self-report of missing one or more oral bisphosphonate doses within the past month) was assessed by kappa statistic

Changes to medication within the same class (e.g., changing from one anti-resorptive medication to prevent osteoporotic fracture to another) will be considered to be a continuation of same medication. The separate classes of medications are listed in appendix A. Since many medications are dispensed with a three month supply at a time, a 15 month follow-up period will be used in order to estimate low levels of compliance during the latter part of first 12 months of the follow-up period. This variable will include only prescription medication and will exclude those taken over the counter, since utilization of over the counter medications cannot be adequately tracked. Since refill records are not a precise measure of how many doses the individual has taken (particularly for the last prescription filled), this will be modeled as a four level ordinal variable.

Primary Independent Variables

Perceived Harm From and Overuse of Medication (Medication Concerns)

The perception that medications are in general harmful and overused will be assessed by a 15 item scale, 12 item of which are the Medication Concerns Scale developed from our preliminary pilot study plus three additional items. Two key advantages of this scale over the specific concerns subscale of Horne and colleagues are first that it assesses the additional component of concerns regarding medication that they are overused, and second that it has been subjected to analyses using item response theory models and appears (in those with osteoporosis) to have good measurement properties across the range of the latent construct. However, we are currently pre-testing three additional items (last three items) that also assess the degree to which a person feels that their personal identity is compromised by having to take medication. The factor structure of the original 12 item instrument, and also of all 15 items together was checked.

Perceived Necessity of Medications

The necessity subscale of the BMQ does have good internal consistency reliability among those with osteoporosis (Cronbach's alpha 0.85) (unpublished data). Since osteoporosis is asymptomatic until and unless a fracture occurs, two of the five items of the BMQ necessity subscale (such as "my life would be impossible without my medicines") lack face validity when considering their osteoporosis medication alone. The remaining three items of the necessity subscale still have reasonable internal consistency reliability (Cronbach's alpha 0.75) among those with osteoporosis. Four additional items specifically worded to assess participants perceptions that medication reduces that risk of fractures will be added to those three to assess perceived necessity of medication in the cohort with osteoporosis.

Relationship with Prescribing Physician

The perceived relationship with the physician prescribing medication for osteoporosis will be assessed for the diabetes and osteoporosis cohorts, respectively, with three scales. The first is the 11 item Trust in Physician scale that assesses the perceived degree that the physician truly cares about the patient and puts his or her needs first, confidence in the physician's judgment and competence, and the degree to which the patient is willing to follow the advice of that physician. Freburger and colleagues showed this scale in factor analyses to be unidimensional, and to have good internal consistency reliability in a mixed population of patients with rheumatoid arthritis, osteoarthritis, and fibromyalgia (Cronbach's alpha equal to 0.87).(251) Thom and colleagues have shown unidimensionality and excellent internal consistency reliability (Cronbach's alpha equal to 0.89) in consecutive primary care patients.(88)

Two specific aspects of patient-provider communication will be also assessed. The first is how open the communication is with the physician from the patient's perspective. This is postulated to directly influence the perceived benefits and risks regarding medicinal therapy for osteoporosis at the end of the medical encounter. *Open communication* will be assessed with a five item scale developed by the American Board of Internal Medicine that has been shown by Heisler and colleagues to have a Cronbach's alpha of 0.93.(80) Open communication has been shown to be correlated with self-reported compliance to medical treatment recommendations by

Hausman(79). The second is the patient's perception of the congruence between themselves and their physician regarding how medical decisions about their care are made. We will first ask the degree to which they themselves exercise decision making power in the relationship with their provider, and then assess their level of satisfaction with that arrangement.

Instrumental Social Support

Instrumental social support refers to specific actions taken by other individuals in one's social network that practically is of aid. For example, organizing medications for the following week into a pill organizer for a frail family member would be an instance of instrumental social support. In our study, we will use an English translation of four items of the original 6-item subscale of Dobbels and colleagues to assess instrumental social support for medication use behavior.(200)

Self-Efficacy Regarding Medication Use Behavior

Even when individuals intend to take medication, there is nonetheless variability in the confidence that individuals have to remember to take medication and execute that behavior in the context of their daily task environment. Self-efficacy refers to the belief that one is capable of achieving or carrying out a behavior or role performance to achieve a desired goal.(252) Self-efficacy has been shown to be associated with a variety of health behaviors.(209, 253) Seven items from the self-efficacy for medication compliance scale (validated in patients with osteoporosis) of Resnick and colleagues will be used to measure this concept.(209) However, after pre-testing this instrument among five patients with osteoporosis, we have changed the scale from a visual analogue to a Likert scale.

Depression

We originally considered depression, conceptualized a co-morbidity, to be important only as a control variable. Because the time of interest with respect to medication use behavior was the prior 18 months, we wanted to emphasize assessment of self-reported depression within that time period, reasoning that depression even for a transient period during that time period conceivably may affect medication use behavior We chose to use the 3 item depression screening subscale of the SF-36D, a variation of the SF-36, because two of the three items specifically assess depressed mood within the past year and within the past 2 years.(254)

Disease Knowledge

A key question corollary question is whether negative attitudes toward medication are associated with poor knowledge regarding the target disease and its impact on health status. Existing measures of patient osteoporosis knowledge tend to assess knowledge of risks factors for low bone mass, rather than knowledge regarding risk of and consequences of fractures.(26, 124, 255) We believe that knowledge of the latter factor is more germane to decision making regarding medication use to prevent fractures. Hence, we constructed a separate 9 item questionnaire, and pre-tested this in a convenience sample of recognized experts within the field of osteoporosis to be sure that there is very strong consensus regarding the correct and incorrect answers to each item. The convenience sample consisted of 13 researchers in the field of osteoporosis attending the annual Steering Committee meeting of the Osteoporotic Fractures in Men (MrOS) Study in November, 2006.

Perceived susceptibility to and severity of osteoporotic fractures

This was assessed by the three items of the four item instrument of Gerend and colleagues, validated in a sample of post-menopausal women. This consists of two items asking for their perceived susceptibility qualitatively to fracture within the next 10 years, and a third one asking for an actual percentage estimate of their fracture risk within the next 10 years. The fourth item asks them to compare their risk to other women their age. A very similar instrument, assessing how susceptible post-menopausal women feel susceptible to osteoporosis, has been shown by Gerend and colleagues to be unidimensional.(256, 257) We have revised this to assess perceived susceptibility to osteoporotic fracture, and dropped on item because in our pre-test with five individuals with osteoporosis will re-establish its dimensionality and measurement properties. Perceived severity (health consequences) of fractures will be assessed by three *ad* hoc items constructed for this study.

Number of Prescribed Doses per Day

This will be included as a surrogate measure of medication regimen complexity, and will be determined from survey self-report. This can be considered a potential barrier to execution of medication use behavior (**Appendix A**)

Perceived Out of Pocket Medication Cost Burden

The degree to which the patient perceives out of pocket costs to be a financial burden will be assessed by one item (**appendix A**)

Patient Characteristics

The survey will also assess the following

- Sex
- Disease Duration (osteoporosis)
- Self-reported prior fracture of the spine, hip, pelvis, wrist, or humerus (upper arm)
- Self-reported prior fracture of the hip or spine in a first degree relative (parent or sibling)
- Income level
- Educational attainment

The table on the following two pages summarizes these variables and how they will be measured. For many the choice of modeling them as ordinal or as interval level variables will depend on their distribution and their scaling properties as demonstrated in our study populations.

Study Population

The inclusion criteria were as follows;

1. Age greater than 21 and less than 85.
2. Signed Park Nicollet general consent allowing for use of medical records for research.
3. Diagnosis of osteoporosis (733.0x).
4. Commencement of oral bisphosphonate medication (alendronate or risedronate) for osteoporosis between the dates of July 1, 2005 and June 30, 2006, according to the Outpatient Medication section of the Park Nicollet electronic medical record.
5. Evidence of a care visit within the last six months (to increase the probability that the person is still a client of our care system).

The exclusion criteria were;

1. A diagnosis of dementia or use of medication (Aricept or Nemenda) to treat dementia.
2. Use of parenteral fracture prevention medications during the study period of January 1, 2006 through March 31, 2007

Table 2-1: Operational Definitions of Variables in Conceptual Model

Variable (Abbreviation)	Definition/Description	Measurement	Data Type
Medication Persistence	Stopped medication for more than one month due side effects or other reasons	Self-Report	Ordinal (2 levels)
Medication Compliance	Number of missing doses over the past month	Self-Report	Ordinal (5 levels)
Medication Concerns	Perception that Medications are Harmful	Self-Report Likert Scale (15 Items)	Ordinal or Interval
Necessity	Perceived Necessity of Medication	Self-Report Likert Scale (7 Items)	Ordinal or Interval
Trust in Physician	Level of Patient's Trust in Physician's Care and Competence	Self-Report Likert Scale (11 Items)	Ordinal or Interval
Provider Open Communication	Patient Perceptions of Provider Communication	Self-Report Likert Scale (5 Items)	Ordinal or Interval
Congruence Regarding Decision Making	Patient Perceptions of shared decision making by provider	Self-Report Likert Items (2 Items)	Ordinal
Perceived Susceptibility to Osteoporotic Fracture	Degree to which patient feels susceptible to fracture	Self-Report Likert Scale (4 Items)	Ordinal of Interval
Perceived Severity of Osteoporotic Fractures	Perceived severity of fractures should they occur	Self-Report Likert Scale (3 Items)	Ordinal or Interval
Depression	Prior experience of depression over the past three years	3 items (score 0-3)	Ordinal
Instrumental Social Support	Reminders and help to take medication	Self-report Likert Scale (4 Items)	Ordinal
Medication Use Self-Efficacy	Perception that one is able to execute medication use behavior	Self-Report Rating (7 Items)	Ordinal or Interval
Disease Knowledge	Level of Knowledge of Disease Complications	Self-Report (9 Items)	Ordinal or Interval
Out of pocket drug cost burden	Perceived financial burden of out of pocket drug cost	Self-report (1 Item)	Ordinal

Variable (Abbreviation)	Definition/Description	Measurement	Data Type
Bone Mineral Density	Worst T-score of Lumbar Spine, Femoral Neck, Total Hip	Medical Record Review	Continuous/Interval
Number of medication doses per day	Number of daily doses for each medication, all added together	Medical Record Review	Interval or Ordinal
Prevalent Vertebral Fracture	Documentation in Report from Densitometric Lateral Spine Image	Medical Record Review	Categorical (3 categories)
Smoking Status	Current, Past, or Never at time of Survey Mailing (Date closest to 7/16/2007)	Medical Record Review	Ordinal (3 levels)
Current Glucocorticoid Use	Use of oral prednisone or equivalent for more than 3 months during period 1/1/06 – 3/31/07	Medical Record Review	Dichotomous
History of Adverse Drug Reactions (ADRs)	Number of Medications to which patient has had an ADR	ADR Section of Medical Record	Ordinal
Proton Pump Inhibitor (PPI) Use	Use of a PPI for more than 1 month during period 1/1/06 – 3/31/07	Medical Record Review	Dichotomous
Personal history of fracture	History of prior hip, wrist, spine, shoulder, or pelvis fracture	Self report (1 Item)	Dichotomous
Family History of Fracture	History of spine or hip fracture in 1st degree relative	Self report (1 item)	Dichotomous
Patient Age	Years since birth date until year of survey return date	Medical Record Review	Interval
Patient Sex		Medical Record Review	Categorical (dichotomous)
Monetary Resources	Monthly Gross Income	Self-report (1 Item)	Ordinal
Education Level	Level of Formal Education	Self-report (1 Item)	Ordinal

Factor Analysis of the Survey Items Assessing Latent Variables

This dataset is from a survey and medical record review of patients given one or more prescriptions for oral bisphosphonate therapy at Park Nicollet Clinic between

the dates of January 1, 2006 and March 31, 2007. Candidate participants were those age 21 to 84 with one or more prescriptions for an oral bisphosphonate medication in the electronic medication record in this time period, who had had a clinic visit within 6 months of the mailing date of the survey (to assure they were still receiving care at Park Nicollet Clinic) and did not have a diagnosis of dementia.

Potential study participants were mailed the survey during the week of July 16 through July 20, 2007. Those who had not returned the survey within two weeks were mailed a reminder postcard. Those who had still not returned the survey or called in to actively refuse participation were mailed a second survey one month later. Among the subset of survey respondents, 59% sent their survey back by July 31, and 97% had returned their survey by August 31, 2007.

Surveys were mailed to all 1179 individuals within the Park Nicollet care system who met all inclusion and exclusion criteria, and 807 were returned, and four surveys were returned as undeliverable. Fifty recipients called back actively refusing participation. Seven of the remaining non-respondents and 13 respondents were excluded because medical record review showed that they had received either intravenous bisphosphonate medication or subcutaneous teriparatide during the period January 1, 2006 through March 31, 2007, were deceased, had never been prescribed an oral bisphosphonate, or had documentation of dementia on further review of their medical record. Sixty-five were excluded because more than one-half of the items for one or more of the scales measuring predictor variables were not answered. The final response rate was 729 of 1159, or 62.9%.

Complete data was present for 510 (70%) and for the remaining 219 participants a mean 1.26 items (of a total of 57) per participant had to be imputed. A univariate imputation model for each missing item using all other items as predictor variables. A posterior distribution for each missing variable was created from these models, and a value for each missing datum was randomly selected from these distributions and imputed into the dataset.

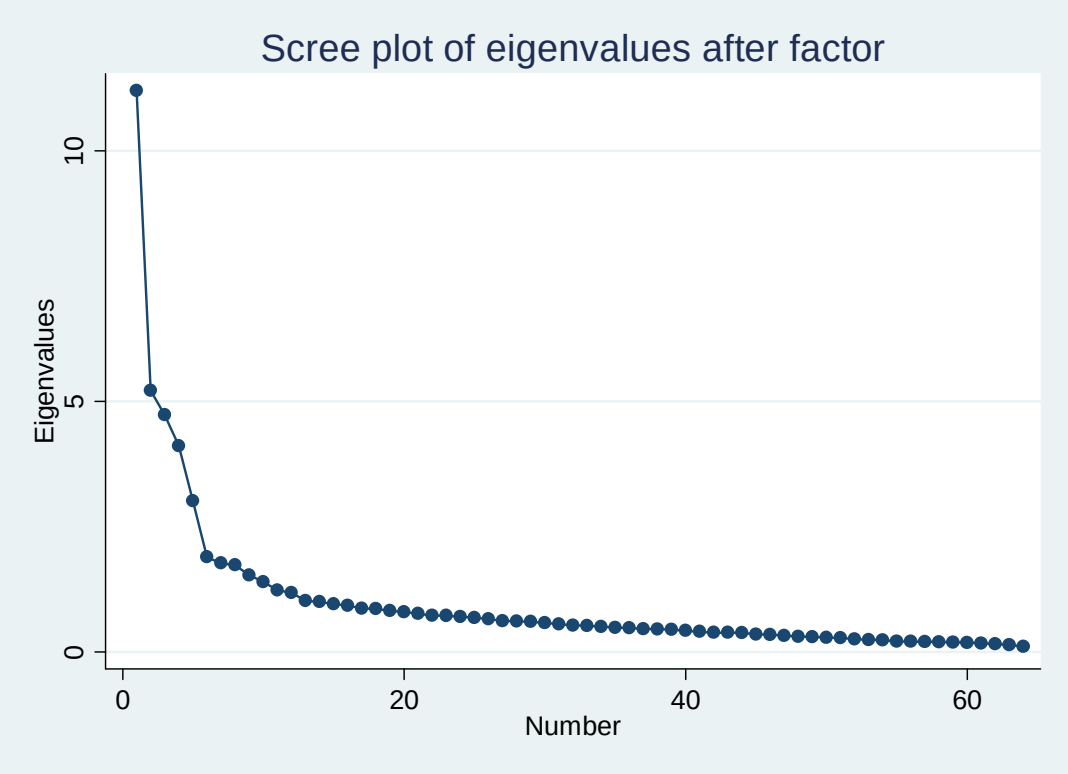
Principal Components Analysis

All of the survey items used in scales to measure latent variables in the model were subjected to factor analysis. This excluded the items in the “About You”, “Taking Osteoporosis Medicines” and “More About You”, and “Help Taking Your

Medications" sections of the survey instrument (**Appendix A**). The "Help Taking Your Medications" section was deleted because 58 individuals chose not to answer any of the items in the scale, and an additional 30 individuals answered only 2 of the 4 items, bringing into question the validity of this scale.

Principal components analysis with orthogonal rotation was done for the remaining items. The scree plot is shown in figure 2. This suggests a five factor solution might be best, there is also a slight further dip in the plot after 8 factors, and hence the factor structure of these items was examined forcing either a five factor or eight factor solution.

Figure 2-2: Scree Plot of Survey Items from Principal Components Analysis



Principal Components Analysis with Five Factors

The rotated factor loadings of the survey items are shown below, with those loadings > 0.3 in blue. The items are labeled according to the title of the scale on the survey instrument (**appendix A**) to which they are purported to belong.

Table 2-2: Factor Loadings of Items with Five Factor Solution

Variable	Factor1	Factor2	Factor3	Factor4	Factor5	Uniqueness
Q1_CONCERNS	-0.0251	-0.0798	0.6323	-0.0643	0.0209	0.5887
Q2_CONCERNS	-0.1010	0.0759	0.5783	-0.1389	0.2470	0.5693
Q3_CONCERNS	0.0113	-0.0649	0.5135	0.0130	-0.0534	0.7289
Q4_CONCERNS	-0.2846	0.0474	0.5473	-0.1070	0.0725	0.6005
Q5_CONCERNS	-0.3127	0.0771	0.6207	-0.1609	0.1121	0.4726
Q6_CONCERNS	-0.1419	-0.0290	0.6002	-0.0734	0.0235	0.6128
Q7_CONCERNS	-0.1084	-0.0254	0.5581	-0.0881	0.0614	0.6646
Q8_CONCERNS	-0.1695	-0.0573	0.6535	-0.0997	0.0509	0.5283
Q9_CONCERNS	-0.1411	-0.1027	0.5420	-0.0939	-0.0694	0.6621
Q10_CONCERNS	-0.0421	-0.1435	0.6056	-0.0583	-0.2006	0.5672
Q11_CONCERNS	-0.0154	-0.1150	0.6542	-0.0647	-0.0959	0.5452
Q12_CONCERNS	0.2081	0.1100	-0.3369	0.1166	-0.0946	0.8086
Q13_CONCERNS	-0.0595	-0.2508	0.5875	0.0711	0.1211	0.5687
Q14_CONCERNS	-0.0560	-0.3099	0.5975	0.1196	-0.0104	0.5294
Q15_CONCERNS	-0.0356	-0.2984	0.5633	0.0869	-0.0348	0.5837
Q1_NEED	0.0799	-0.0013	0.0061	0.6960	-0.0171	0.5089
Q2_NEED	0.0889	0.0436	-0.0414	0.7040	0.0555	0.4898
Q3_NEED	0.1622	0.1476	-0.1558	0.5811	-0.0037	0.5900
Q4_NEED	0.0617	0.0926	-0.0021	0.7558	0.1134	0.4035
Q5_NEED	0.0716	0.0842	-0.0506	0.7990	0.1389	0.3275
Q6_NEED	0.1562	0.1230	-0.1647	0.6832	0.0414	0.4649
Q7_NEED	0.1806	0.1234	-0.1198	0.6930	-0.0101	0.4575
Q1_DOCTOR	0.7165	0.0796	-0.0024	0.0331	0.0366	0.4778
Q2_DOCTOR	0.7545	0.0982	-0.0555	0.0683	0.0122	0.4132
Q3_DOCTOR	0.7299	0.0999	-0.0755	0.1603	-0.0716	0.4208
Q4_DOCTOR	0.5474	-0.0478	-0.0782	0.2090	-0.1584	0.6232
Q5_DOCTOR	-0.5527	0.0089	0.1671	-0.0861	0.0930	0.6504
Q6_DOCTOR	0.6588	0.0752	-0.1426	0.1449	-0.0400	0.5174
Q7_DOCTOR	-0.6418	-0.0711	0.1228	0.0333	-0.0051	0.5669
Q8_DOCTOR	0.6547	0.0749	-0.0189	0.0992	-0.0636	0.5515
Q9_DOCTOR	0.6679	0.1082	-0.0489	0.0735	0.0609	0.5307
Q10_DOCTOR	0.6633	0.1050	-0.0327	0.0879	-0.0828	0.5334
Q11_DOCTOR	-0.4401	-0.1251	0.1164	0.0554	-0.0723	0.7688
Q1_INFORM	0.7689	0.1760	-0.0788	0.0209	0.0709	0.3661
Q2_INFORM	0.6980	0.1690	-0.0523	-0.0355	0.1036	0.4695
Q3_INFORM	0.7880	0.1447	-0.0376	0.0276	0.0097	0.3558
Q4_INFORM	0.7703	0.1119	-0.1172	0.0259	-0.0286	0.3789
Q5_INFORM	0.7973	0.1280	-0.0740	0.0611	-0.0348	0.3375
Q2_DECISIONS	0.5779	0.0999	-0.0502	-0.0171	0.0548	0.6503
Q1_CHANCE	-0.1028	-0.2079	0.1192	0.3851	0.2424	0.7249
Q2_CHANCE	-0.1171	-0.1707	0.1034	0.3993	0.3793	0.6432
Q3_CHANCE	-0.1593	-0.0962	0.0474	0.3768	0.3075	0.7266
Q1_HEALTH	-0.0241	-0.0167	-0.0057	0.1875	0.5844	0.6224
Q2_HEALTH	0.0230	-0.0416	0.0191	0.2773	0.6336	0.5190
Q3_HEALTH	0.0391	-0.0199	0.0603	0.2674	0.6308	0.5251
Q1_SHED	0.1028	0.8427	-0.0768	0.0712	0.0375	0.2669
Q2_SHED	0.1511	0.7932	-0.0554	0.0344	-0.0382	0.3424
Q3_SHED	0.1124	0.8211	-0.0153	0.0516	-0.0467	0.3082
Q4_SHED	0.1324	0.8801	-0.0877	-0.0029	0.0168	0.2000
Q5_SHED	0.1180	0.8718	-0.0557	0.0354	-0.0339	0.2205
Q6_SHED	0.0541	0.8003	-0.0655	0.0800	0.0286	0.3451
Q7_SHED	0.1625	0.7717	-0.0295	0.0941	-0.0834	0.3614
Q1_DEPRESS	0.1217	0.3179	-0.2002	-0.2797	-0.0032	0.7658
Q2_DEPRESS	0.0971	0.2106	-0.2241	-0.1773	0.0771	0.8586
Q3_DEPRESS	0.1635	0.2566	-0.1803	-0.2314	0.1350	0.8032
q1know	0.0069	0.0206	-0.0753	0.0428	0.2684	0.9200
q2know	-0.0500	-0.1770	0.0501	0.0755	0.3257	0.8519
q3know	0.0289	0.0701	-0.1520	0.0517	0.4162	0.7953
q4know	-0.0161	0.0235	0.0284	0.0674	0.4941	0.7497
q5know	0.0017	-0.0509	0.0601	0.0177	0.5533	0.6873
q6know	0.0017	-0.0860	0.0587	-0.0324	0.5704	0.6628
q7know	0.0045	-0.0197	0.0528	-0.0134	0.4671	0.7784
q8know	-0.0062	-0.0091	-0.0379	-0.0809	0.5291	0.7119
q9know	-0.0510	0.0281	-0.0245	-0.0195	0.5220	0.7231

With a forced five factor solution, the 15 Concerns items all map to factor 3, with no other items mapping to this factor. The items of the Trust in Physician scale (Q1_Doctor through Q11_Doctor), the five items of the Provider Open Communication scale (Q1_Inform through Q5-Inform), and the 1 item assessing satisfaction with provider decision making style all mapped to factor1. The first two items of the knowledge scale (q1know and q2 know) and two of the three depression items did not map to any factor.

The five factor solution implies that the 3 items that assess perceived susceptibility to fracture (Q1_Chance through Q3_Chance) can be grouped with the need items, or that the fracture knowledge, chance of fracture, and perceived severity of fractures (health) might be one construct. The following principal components analysis of the 7 need and 3 chance items together, however, suggest that together they do *not* form a unidimensional scale. The ratio of the first to second eigenvalues is only 2.07, and when a 2 factor solution is forced on these 10 items, two factors clearly emerge with the 7 need items loading on one and the 3 chance items loading on another.

Table 2-3: Eigenvalues from Principal Components Analysis of 7 Need and 3 Chance Items

Factor analysis/correlation — Number of obs = 742
Method: principal-component factors — Retained factors = 2
Rotation: (unrotated) — Number of parameters = 19

Factor	Eigenvalue	Difference	Proportion	Cumulative
Factor1	4.28155	2.21760	0.4282	0.4282
Factor2	2.06395	1.16565	0.2064	0.6346
Factor3	0.89830	0.25724	0.0898	0.7244
Factor4	0.64106	0.08992	0.0641	0.7885

Figure 3 – Scree Plot of PCA of 7 Need and 3 Chance Items

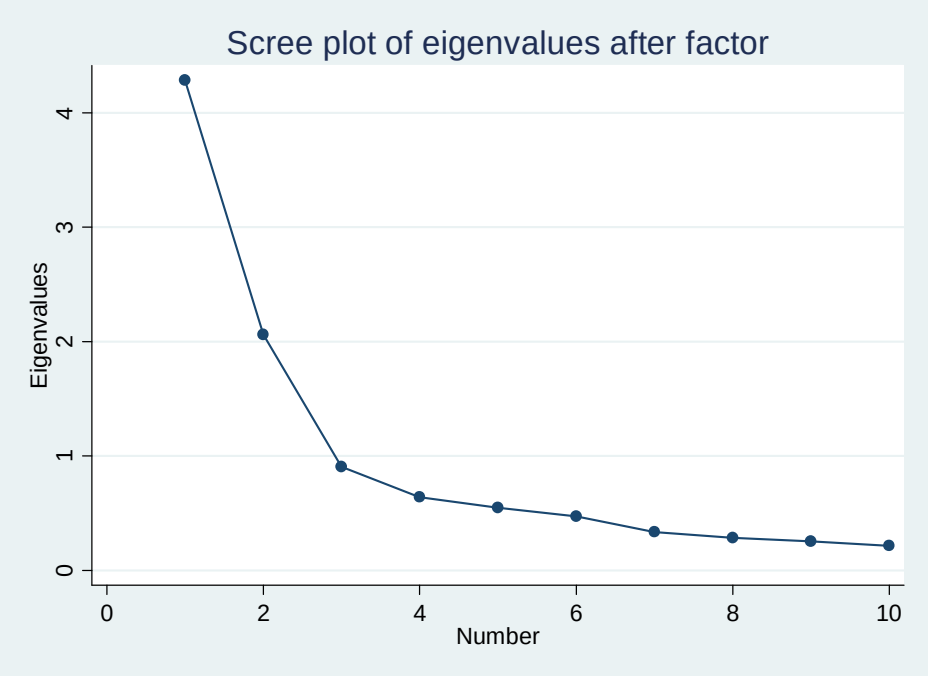
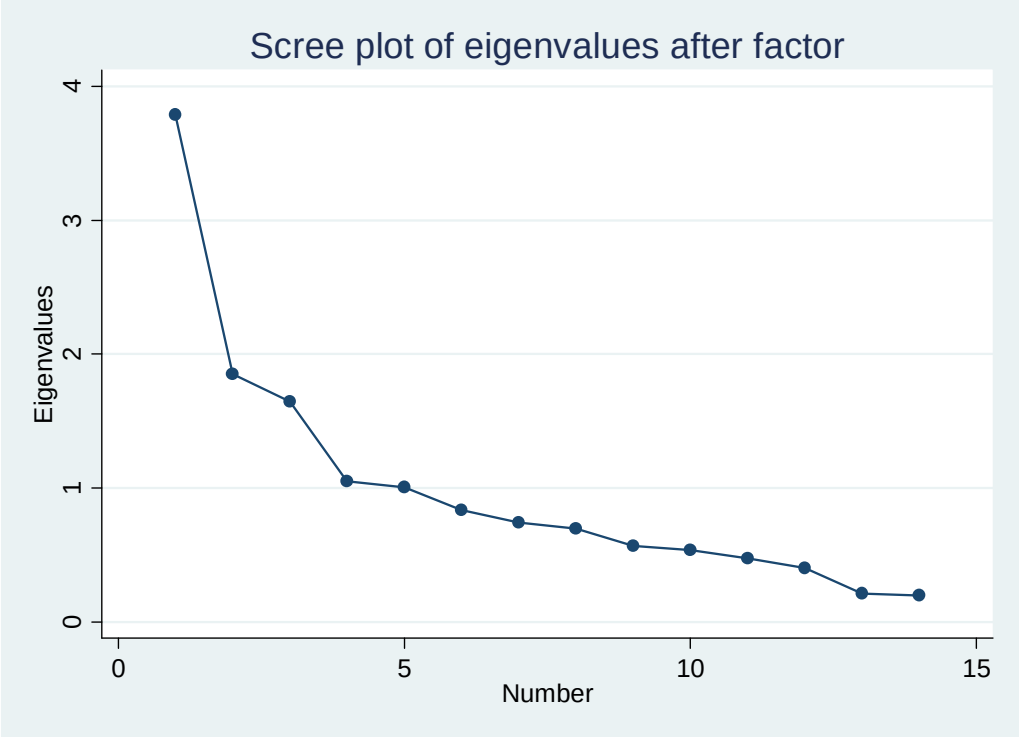


Table 2-4: Rotated factor loadings of 7 Need and 3 Chance Items

Variable	Factor1	Factor2	Uniqueness
Q1_NEED	0.6633	0.1752	0.5293
Q2_NEED	0.7171	0.1484	0.4637
Q3_NEED	0.7413	-0.1333	0.4327
Q4_NEED	0.7335	0.2827	0.3821
Q5_NEED	0.7663	0.3352	0.3004
Q6_NEED	0.8068	-0.0023	0.3490
Q7_NEED	0.8057	-0.0091	0.3507
Q1_CHANCE	0.0454	0.8831	0.2181
Q2_CHANCE	0.0706	0.8997	0.1856
Q3_CHANCE	0.1400	0.7332	0.4428

Similarly, when the items comprising the fracture knowledge, perceived susceptibility to, and perceived severity (health consequences) of fractures are assessed with a principal components analysis separate from the other survey items, the scree plot itself supports either a one factor or a 3 factor solution.

Figure 2-4: Scree Plot of Knowledge, Fracture Susceptibility (Chance) and Fracture Severity (Health) Items



However, the ratio of the first to second eigenvalue is only 1.98, suggesting that a 3 factor solution may be better. The rotated factor loadings of a three factor solution are as follows.

Table 2-5: Rotated Factor Loadings for 3-Factor Solution of Knowledge, Fracture Susceptibility (Chance) and Fracture Severity (Health) Items

Variable	Factor1	Factor2	Factor3	Uniqueness
q2know	0.2351	0.3551	0.0260	0.8180
q3know	0.2472	0.2461	0.1724	0.8486
q4know	0.2182	0.5027	0.0775	0.6937
q5know	0.1885	0.6106	0.0867	0.5840
q6know	0.2208	0.6325	0.0216	0.5507
q7know	-0.0062	0.6793	0.0775	0.5325
q8know	0.0121	0.6948	0.0798	0.5107
q9know	0.1658	0.5090	0.1156	0.7000
Q1_HEALTH	0.8176	0.0422	0.1122	0.3171
Q2_HEALTH	0.8931	0.0909	0.1314	0.1769
Q3_HEALTH	0.8940	0.0827	0.0949	0.1849
Q1_CHANCE	0.0626	0.0054	0.8909	0.2024
Q2_CHANCE	0.1864	0.0776	0.8868	0.1728
Q3_CHANCE	0.0897	0.0897	0.7489	0.4231

Hence, these results suggest that perceived need for fracture prevention medication (Need) and perceived susceptibility to fractures do not comprise only one construct, and that fracture knowledge, perceived susceptibility to fractures (Chance) and perceived severity of fractures (Health) do not comprise one construct. Therefore, it is quite likely that there are more than five factors among all of these survey items.

Principal Components Analysis with an 8 Factor Solution

Table 2-6: Rotated Factor Loadings of all Survey Scale Items with 8 Factor Solution

Variable	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6	Factor7	Factor8
Q1_CONCERNS	-0.0078	-0.0872	**0.5837**	-0.0610	0.0599	0.2961	0.0116	-0.0816
Q2_CONCERNS	-0.0950	0.0579	**0.5787**	-0.1114	0.0915	0.1088	0.2518	-0.0027
Q3_CONCERNS	0.0300	-0.0789	**0.5535**	-0.0379	0.0669	0.0266	-0.2000	0.1383
Q4_CONCERNS	-0.2939	-0.0122	**0.6183**	-0.0328	0.0300	-0.0160	0.0604	-0.0577
Q5_CONCERNS	-0.3000	0.0269	**0.6932**	-0.1079	0.0279	-0.0403	0.0923	-0.0096
Q6_CONCERNS	-0.1229	-0.0734	**0.6448**	-0.0701	0.0121	0.0128	-0.0377	0.0755
Q7_CONCERNS	-0.1014	-0.0571	**0.6052**	-0.0678	0.0645	-0.0057	0.0261	0.0454
Q8_CONCERNS	-0.1503	-0.0710	**0.6545**	-0.1084	-0.0209	0.1008	0.0414	0.1028
Q9_CONCERNS	-0.1401	-0.1236	**0.5530**	-0.0565	-0.1314	0.1098	0.0261	0.0158
Q10_CONCERNS	-0.0209	-0.1324	**0.5819**	-0.0951	-0.1340	0.1825	-0.1793	0.0933
Q11_CONCERNS	0.0014	-0.1285	**0.6533**	-0.0511	-0.0722	0.1453	-0.0715	0.0051
Q12_CONCERNS	0.1812	0.0896	**-0.3401**	0.1429	0.1038	-0.0612	-0.1655	-0.1713
Q13_CONCERNS	-0.0610	-0.1800	**0.4120**	-0.0128	0.1339	**0.5519**	0.1211	-0.0256
Q14_CONCERNS	-0.0621	-0.2315	**0.4088**	0.0362	0.0929	**0.6251**	0.0079	-0.0914
Q15_CONCERNS	-0.0387	-0.2027	**0.3537**	-0.0203	0.0619	**0.6586**	-0.0028	-0.0663
Q1_NEED	0.0762	-0.0004	-0.0240	**0.6608**	0.0703	0.1317	-0.0896	0.1533
Q2_NEED	0.0770	0.0320	-0.0423	**0.7219**	0.0997	0.0595	-0.0157	0.0852
Q3_NEED	0.1244	0.0989	-0.0907	**0.7271**	0.0813	-0.0592	0.0120	-0.1485
Q4_NEED	0.0637	0.0864	-0.0196	**0.7302**	0.0578	0.0691	0.0627	0.2581
Q5_NEED	0.0713	0.0800	-0.0572	**0.7659**	0.0977	0.0363	0.0645	0.2874
Q6_NEED	0.1289	0.0765	-0.1063	**0.7832**	0.0732	-0.0711	0.0319	-0.0331
Q7_NEED	0.1567	0.0793	-0.0823	**0.7903**	0.0798	-0.0389	-0.0238	-0.0152
Q1_CHANCE	-0.0357	-0.1191	0.0503	0.1018	0.0854	0.0567	0.0084	**0.8455**
Q2_CHANCE	-0.0580	-0.0857	0.0358	0.1157	0.2086	0.0416	0.0871	**0.8431**
Q3_CHANCE	-0.1190	-0.0505	0.0127	0.2083	0.1002	0.0208	0.1574	**0.6241**
Q1_HEALTH	-0.0342	-0.0034	-0.0261	0.0779	**0.8082**	-0.0071	0.0636	0.0912
Q2_HEALTH	0.0087	-0.0175	-0.0029	0.1261	**0.8610**	0.0347	0.0740	0.1410
Q3_HEALTH	0.0227	-0.0102	0.0483	0.1402	**0.8584**	0.0182	0.0808	0.0959
Q1_DOCTOR	**0.7316**	0.0926	-0.0017	-0.0105	0.0578	-0.0152	-0.0479	0.0673
Q2_DOCTOR	**0.7596**	0.1127	-0.0743	0.0425	0.0675	0.0062	-0.0503	0.0110
Q3_DOCTOR	**0.7363**	0.1258	-0.0953	0.1224	0.0632	0.0338	-0.1691	0.0078
Q4_DOCTOR	**0.5464**	-0.0296	-0.0844	0.1575	0.0291	-0.0076	-0.2686	0.0609
Q5_DOCTOR	**-0.5501**	0.0003	0.1651	-0.0840	0.0427	0.0556	0.1129	-0.0048
Q6_DOCTOR	**0.6510**	0.0740	-0.1507	0.1533	0.0417	-0.0067	-0.0681	-0.0581
Q7_DOCTOR	**-0.6231**	-0.0599	0.1158	0.0280	-0.0798	0.0934	0.0461	0.0556
Q8_DOCTOR	**0.6775**	0.0816	-0.0120	0.0867	0.0025	-0.0559	-0.1302	0.0547
Q9_DOCTOR	**0.6653**	0.1025	-0.0453	0.0733	0.1301	-0.0387	-0.0211	-0.0333
Q10_DOCTOR	**0.6725**	0.1031	-0.0208	0.0936	-0.0840	-0.0492	-0.0515	0.0350
Q11_DOCTOR	**-0.4215**	-0.0760	0.0660	-0.0552	-0.0167	0.1351	-0.1344	0.1943

Variable	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6	Factor7	Factor8
Q1_INFORM	**0.7695**	0.1641	-0.0887	0.0805	-0.0072	-0.0556	0.1199	-0.0952
Q2_INFORM	**0.6876**	0.1588	-0.0316	0.0020	0.0722	-0.0785	0.0957	-0.0950
Q3_INFORM	**0.7917**	0.1439	-0.0503	0.0720	-0.0607	-0.0321	0.0812	-0.0531
Q4_INFORM	**0.7716**	0.1042	-0.1144	0.0763	-0.1164	-0.0565	0.0753	-0.0487
Q5_INFORM	**0.7992**	0.1148	-0.0693	0.1062	-0.0942	-0.0444	0.0465	-0.0316
Q1_SHED	0.1016	**0.8339**	-0.0361	0.0932	0.0329	-0.1371	0.0298	-0.0437
Q2_SHED	0.1522	**0.8134**	-0.0562	0.0378	-0.0455	-0.0300	-0.0029	-0.0563
Q3_SHED	0.1241	**0.8606**	-0.0407	0.0119	-0.0656	0.0269	-0.0057	0.0295
Q4_SHED	0.1285	**0.8675**	-0.0355	0.0360	0.0278	-0.1593	0.0116	-0.0902
Q5_SHED	0.1197	**0.8892**	-0.0513	0.0275	0.0033	-0.0626	-0.0427	-0.0461
Q6_SHED	0.0450	**0.8160**	-0.0722	0.0686	0.0521	-0.0446	0.0057	-0.0289
Q7_SHED	0.1642	**0.7755**	-0.0169	0.1000	-0.0511	-0.0481	-0.0627	-0.0364
Q1_DEPRESS	0.1164	0.1867	0.0446	-0.0881	-0.0323	**-0.6161**	-0.0140	-0.2050
Q2_DEPRESS	0.0872	0.0774	0.0104	0.0053	0.0351	**-0.6105**	0.0294	-0.1350
Q3_DEPRESS	0.1488	0.1254	0.0858	-0.0362	0.1370	**-0.6173**	0.0287	-0.2028
q1know	-0.0180	-0.0240	-0.0107	0.1114	0.2214	-0.1553	0.1851	-0.0664
q2know	-0.0585	-0.1659	0.0250	0.0635	0.2304	0.0930	0.2513	0.0361
q3know	0.0276	0.0778	-0.1491	0.0132	0.2645	-0.0780	0.2827	0.1606
q4know	-0.0223	0.0182	0.0334	0.1007	0.2010	-0.0041	**0.4790**	0.0846
q5know	0.0002	-0.0479	0.0396	0.0529	0.1869	0.0651	**0.5830**	0.0723
q6know	0.0011	-0.0600	0.0135	-0.0126	0.2319	0.1460	**0.5961**	0.0129
q7know	0.0209	-0.0364	0.0710	0.0488	-0.0034	-0.0368	**0.6079**	0.1361
q8know	0.0020	-0.0363	0.0030	-0.0029	0.0354	-0.1219	**0.6442**	0.1324
q9know	-0.0540	0.0337	-0.0487	0.0016	0.2070	0.0514	**0.5335**	0.0446

As can be seen from this table, knowledge questions q1know, q2know, and q3 know do not load onto any factor, and the last three items of the Concerns scale map onto two domains. If these five items are eliminated, however, the factor loadings of the rest of the items comprise a simple factor structure. Therefore, in the subsequent analyses, Concerns about medications is measured with items Q1_Concerns through Q12_Concerns, and fracture knowledge with items q4 know through q9know.

A confirmatory factor analysis this simple structure of 8 factors was also done using MPLUS 5.1. While the goodness of fit as judged by the Comparative Fit Index (CFI) was not optimal at 0.835, the goodness of fit to the data was reasonable as judged by the Root Mean Square Error of Approximation (RMSEA) value of 0.055 (90% C.I. 0.054-0.057). Similarly, the fit of this simple factor structure to the data was also reasonable as judged by the Standardized Root Mean Square Error (SRMR) value of 0.051.

When each of these 8 scales is examined separately with a principal components analysis, internal consistency reliability of each is quite very good, with the

exception of the fracture knowledge and depression scales which have marginally acceptable internal consistency reliability (**table 2-7**).

Table 2-7: Internal Consistency Reliability and 1st to 2nd Eigenvalue Ratios of 8 Scales

Construct	Number of Scale Items	Ratio of 1st to 2nd Eigen Value	Internal Consistency Reliability (Cronbach's α)
Patient-Provider Relationship Quality	17	5.74	0.93
Medication Necessity	7	4.46	0.87
Medication Concerns	12	3.91	0.85
Medication Use Self-Efficacy	7	10.96	0.94
Perceived Fracture Susceptibility	3	3.81	0.81
Perceived Fracture Severity	3	5.63	0.87
Fracture Knowledge	6	2.53	0.70
Depression	3	3.04	0.69

With the exception of the fracture knowledge scale, the ratio of the first to second eigenvalue of each is greater than 3.0, providing good evidence for each of these seven scales of unidimensionality. These data provide strong evidence that Trust in Physician, Open Provider Communication, and Satisfaction with Provider Decision Making Style are all part of the same construct. In the 3 papers to follow, these 17 items together will comprise the measurement tool for the Patient-Provider Relationship Quality.

As will be seen in the 3 papers to follow, inclusion of depression and fracture knowledge are necessary to achieve good model fit in the multivariate path models. The main study aims (thankfully) of this project are not centered on the association of fracture knowledge and/or depression with fracture prevention medication use

behavior. Nonetheless, a limitation of this project is that these variables have not been optimally measured. Their inclusion as control variables in the analyses to follow will be only to achieve good model fit, and firm conclusions as to their role in medication use behavior will not be drawn.

Chapter 3:
Predictors of Non-Persistence and Non-Compliance with Fracture Prevention Medication due to Side Effects or Other Reasons

Abstract

Background: Non-persistence and non-compliance with oral medication to prevent osteoporotic fracture is widespread and attenuates the fracture reduction benefit that otherwise might be achievable with use of these medications. Perceived need for medication and concerns regarding long-term harm and/or dependence upon medications have been shown to be associated with medication use behavior in several other chronic diseases, but this framework as a predictor of fracture prevention medication use behavior has never been investigated. Moreover, the association of these medication attitudes with medication use behavior independent of other medication attitudes such as medication use self efficacy and perceived medication cost burden as well as objective indicators of fracture risk such as bone mineral density and fracture history has to date not been reported. We postulated that perceived medication need and medication concerns would be associated, respectively, negatively and positively with non-persistence and non-compliance (missed doses) to pharmacologic fracture prevention medication. We also postulated that concerns about the long-term safety of and dependence upon medications in general would be negatively associated with perceived need for fracture prevention medication to preserve health, and therefore would have an additional indirect effect on medication use behavior.

Methods: We surveyed all 1155 individuals age 21 to 84 with a medical record documentation of being given a prescription for an oral bisphosphonate medication to prevent fracture between 1/1/2006 and 3/31/2007 at a large community group practice in the Minneapolis-St Paul metropolitan area. 729 returned valid surveys, and their medical records were reviewed. Medication concerns and perceived necessity for fracture prevention medication were assessed, respectively, with 12-item and 7-item scales. Medication persistence and compliance were assessed by self-report. The direct effects of these attitudes were assessed with logistic regression models, and the total effect of concerns about medication on medication use behavior (direct and indirect through perceived necessity for fracture prevention medication) was assessed with multivariate path models.

Results: Self-reported non-persistence due to side effects was associated with perceived need for medication (odds ratio [OR] of 0.53 per standard deviation increase), medication concerns (OR of 1.23 per standard deviation increase), and 2 or

more adverse drug reactions to any medications recorded in the medical record (OR 3.24 vs. no ADRs). Non-persistence for reasons other than side effects was associated with perceived medication need (OR 0.24 for top vs. bottom quartile), with poor medication use self-efficacy (OR 1.73 vs. excellent self-efficacy) and with high medication cost concerns (OR of 4.85 vs. no cost concerns). Among those with a current prescription for oral bisphosphonate therapy at the time of the survey, non-compliance was associated with medications concerns (OR 1.24 per unit increase) and medication use self-efficacy (OR 0.38). The quality of the patient-provider relationship was not associated directly with non-persistence or non-compliance, adjusting for all of these other predictors. A one standard deviation increase and decrease in perceived need for fracture prevention medication and concerns about medications would be predicted to decrease self-reported non-persistence, respectively, by 33% and 18%. In contrast, changes in perceived need for medication has minimal effects on non-compliance (missing doses), whereas a 1 standard deviation decrease in medication concerns reduced non-compliance by 21%, and a change of medication use self-efficacy category from low to high reduced non-compliance by 32%.

Conclusion: Perceived necessity for fracture prevention medication has a substantial effect on non-persistence with that medication independent of other predictors, but has little effect on non-compliance (missed doses). Patients are less likely to report non-persistence with medications due to side effects if they have feel they need fracture prevention medication to preserve their health, do not have concerns about long-term safety or dependence on medications, have not had other adverse drug reactions, and are not on a proton pump inhibitor. Patients are less likely to discontinue oral bisphosphonates for reasons other than side effects if they have confidence they can execute mediation use in their daily lives (medication self-efficacy) and do not feel burdened by their out of pocket medication costs. Assessing whether or not patients have a realistic appraisal of their need for fracture prevention medication, soliciting and addressing their concerns about medications, reducing their perceived medication cost burden, and improving their medication use self-efficacy all may improve persistence with and compliance to fracture prevention medication.

Introduction

Fractures related to osteoporosis are a major public health problem. Over 1.5 million older individuals in the United States experience a fracture of the hip, spine, wrist, or upper arm, often with permanent adverse effects upon their quality of life.(258) Women and men age 60 have, respectively, a 44% and 29% chance of experiencing a fracture related to osteoporosis sometime in their remaining lifetime.(259) Medications are available that have been shown to reduce the risk of fractures 30% to 50% among those who have osteoporosis by bone density criteria or who already have had a vertebral fracture.(14, 260-264) However, numerous large studies have shown that only 30% to 60% of those prescribed a fracture prevention medication are still taking medication one year later.(28, 29) Medication use behavior has been conceptualized as having two components; *persistence* with medication, defined as not stopping medication prematurely for extended periods of time, and *compliance* defined as taking medications at the prescribed times, in the prescribed dose, and prescribed manner.(1) Those at high risk of fracture who do not persist with fracture prevention medication experience more fractures than those who do persist and comply with those medications.(34, 59, 63)

While numerous studies (primarily through large pharmacy claims databases) have described the extent and time course of the phenomenon, very few studies have attempted to explain the phenomenon. Three studies have shown that attitudes regarding fracture prevention medication influence use of those medications.(41, 58, 265) The perceived effectiveness of fracture prevention medication and concerns about the long-term safety of medications have been shown in one study to be associated with fracture prevention medication compliance, independent of side effects and other predictors.(41)

Horne and colleagues have postulated that medication use behavior can be conceptualized as being driven primarily by their perceptions that specific medications are necessary to maintain or improve their health and by concerns that they may have regarding potential overuse of medications, and the long-term safety of and dependence upon medications.(266, 267) This necessity-concerns framework has been shown to be associated with medication use behavior among patients with heart failure and other cardiac diseases, diabetes mellitus, renal failure, depression, asthma, and acquired immune deficiency syndrome (AIDS). Subsequently, Horne and others

have suggested that medication compliance can be conceptualized as either being intentional or unintentional.(211, 237, 268) Patients who stop taking medication for an extended period of time (non-persistence) generally do so intentionally. Other instances of taking medication differently than as prescribed (such as skipping doses or taking them at different times than instructed, e.g. non-compliance) may occur either intentionally or unintentionally.

Carr and colleagues found a modest association between self-reported medication non-compliance (defined as taking less or more medication than prescribed or missing doses) with concerns about the long-term safety of and dependence upon medication.(265) However, no study to date has investigated whether or not the necessity-concerns conceptual framework of Horne and colleagues may explain fracture prevention medication use behavior among those at high risk of osteoporosis and/or osteoporotic fracture. Moreover, no study has investigated whether or not this framework predicts medication use behavior independent of other medication attitudes (such as medication cost burden and medication use self-efficacy) or objective indicators of fracture risk, or whether or not the associations of these predictors with fracture prevention non-persistence due to side effects are different than non-persistence due to reasons other than side effects. Furthermore, no one to date has differentiated the associations of these predictors with non-persistence (stopping the medication altogether) and other types of non-compliance (persisting with medication but not taking the medication as prescribed). If the model of Horne and colleagues is a valid explanatory framework for medication use behavior among those prescribed fracture prevention medication, then improvement of persistence and compliance with fracture prevention medication may require more detailed assessment of these attitudes than what is typically done during clinical encounters assessment when new medications are prescribed. Specifically, when fracture prevention medications are prescribed, providers may need to assess how patients' view their fracture risk and the effectiveness of medication to reduce that risk, and address their concerns regarding long-term safety of and dependence upon these medications.

Finally, Horne and colleagues have postulated that perceived need for specific medications and concerns about medications are not correlated, have opposite effects on medication use behavior, and therefore propose that the medication need – medication concerns differential (the difference in raw scores between them) is the

best way of conceptualizing the association between these medication attitudes and medication use behavior. However, this formulation does not allow assessment of the relative magnitudes of the effects of these two attitudes on medication use behavior. Moreover, concerns about the long-term safety of and dependence upon medications in general could certainly lead an individual to conclude that their use is *not* needed to maintain their future health even if they believe they are at risk of the target condition for which the medication is prescribed. This raises the possibility that medication concerns may have two effects on medication use behavior, both a direct effect and an indirect effect by reducing perceived need for medication.

The primary aim of this survey and medical record review study was to estimate the associations of perceived necessity for fracture prevention medication and concerns about long-term harm from or dependence upon medication on four measures of fracture prevention medication use behavior (overall non-persistence, non-persistence due to side effects, non-persistence for reasons other than side effects, and among persisters, missed doses). Secondary aims were to also assess the association of medication use self-efficacy and perceived medication cost burden with medication use behavior, and to assess whether or not the influence of medication concerns on medication use behavior includes an indirect effect through perceived need for fracture prevention medication. Additional aims were to assess predictors of perceived necessity of and concerns about medications and the influence of the patient-provider relationship quality on medication use behavior, but these will be addressed in separate publications.

Methods

This study was reviewed and approved by the Institutional Review Boards of both Park Nicollet Heath Services and the University of Minnesota.

This dataset is from a survey and medical record review of patients given one or more prescriptions for oral bisphosphonate therapy at Park Nicollet Clinic between the dates of January 1, 2006 and March 31, 2007. Candidate participants were those age 21 to 84 with one or more prescriptions for a bisphosphonate medication in the electronic medication record in this time period, who had had a clinic visit within 6 months of the mailing date of the survey (to assure they were still receiving care at

Park Nicollet Clinic), and did not have a diagnosis of dementia. Surveys were mailed from July 16 through July 20, 2007.

Conceptual Framework

We conceived of both perceived need for fracture medication and concerns about the long-term safety of and dependence upon medication as predictors of medication use behavior in the context of a variation of the Health Belief Model. Perceived need for medication is postulated to be a driven by perceived susceptibility to the target event, the severity (health consequences) of the target event should it occur, and incorporates as well the patient's perceived effectiveness of the medication to reduce the likelihood of the target event's occurrence or its severity. Consistent with the Health Belief Model, we also postulate that lack of medication use self-efficacy and medication cost concerns would pose significant barriers to medication compliance (**figure 2-1, page 35**).

The Health Belief Model does not specifically postulate a role for concerns regarding medication, and we have added this to the model as a predictor of medication use behavior. Unlike the model of Horne and colleagues, we postulated a direct effect of concerns on perceived medication need (**figure 2-1**). The construct of medication need encompasses the patient perception that maintenance of their health depends on use of a specific medication, but those who have concerns about the long-term safety of medications in general may conclude that their health is *not* dependent on use of medication, even if they perceive they are at risk of the target condition and that the medication reduces that risk.

Since perceived need for medication and concerns about medications are endogenous predictors of medication use behavior in this model, we have also shown postulated upstream predictors of perceived necessity for medication that can be used as instruments for perceived medication necessity (statistical analysis, page 10 to 12). These include objective indicators of fracture risk (personal history of fracture, family history of fracture, bone mineral density, prevalent vertebral fracture, systemic glucocorticoid use, smoking status) and demographic variables (including age, sex, income, and educational status). Additional exogenous variables that directly or indirectly are postulated to be associated with perceived need for fracture prevention medication include the number of daily doses of prescribed medication each day and the patient-provider relationship quality (**figure 2-1**).

Latent variables in the model measured with survey instruments are in black, and other variables are in blue (**figure 2-1)**. Where possible, scales to measure these constructs were derived from previously validated scales, but for some constructs we were unable to find any appropriate measures and hence for these we developed new scales. The unidimensionality of these scales was assessed using principle components analysis of all scale items together, and also from principle components analyses of each scale separately. A ratio of the first to second eigenvalue of greater than 3.0 was considered to be strong evidence of unidimensionality for each scale.

Dependent Variables

Self-reported persistence was assessed with two questions; whether or not the patient had stopped taking their oral bisphosphonate for more than one month due to side effects, whether or not the patient had stopped taking their oral bisphosphonate for more than one month for reasons other than side effects. A variable of self-reported non-persistence for any reason was created if they answered "yes" to either question.

Non-compliance was defined as missing one or more doses of oral bisphosphonate medication over the past month by self-report. Since these variables were assessed retrospectively, of necessity assessment of compliance was limited to those currently prescribed oral bisphosphonate medication at time of the survey.

Predictor Variables – from survey items

The *quality of the patient-provider relationship* was assessed with two previously validated scales; the 11 item Trust in Physician scale (assessing trust in the physician's competence and willingness to address the patient's concerns),(87, 88) the 5 item Open Communication Scale of the Medical Outcomes Study,(80) plus one *ad hoc* item assessing satisfaction with the decision making style of the provider. Factor analysis revealed that all 17 items strongly load on the same factor and together exhibited strong internal consistency reliability and unidimensionality (**table 2-7, page 53**), and thence all were used together to assess the quality of the physician-provider relationship from the patient's perspective.

Perceived necessity of fracture prevention medication was assessed by a seven item scale, adapted from the validated four item medication necessity scale of

Horne and colleagues,(266) with three additional items added to improve its internal consistency reliability and to assess perceived effectiveness of the medication to reduce fracture. *Medication concerns* was measured by a 12-item scale that assessed patient perceptions regarding the perceived long-term safety of and dependence upon medications, and whether or not medications in their view are over-prescribed. This scale was developed from three subscales of the Beliefs about Medications Questionnaire that assess concerns regarding medications that have specifically been prescribed for the patient, concerns that medications in general are harmful, and concerns that medications in general are overprescribed.(142) However, principle components analysis within our sample showed these to all be measuring the same construct, with high internal consistency reliability (**table 2-7**).

Perceived susceptibility to fracture was assessed with 3 items of Gerand and colleagues(256) and *perceived severity of fractures* was also assessed with 3 items developed for this study. We postulated that perceived susceptibility to fractures would not be associated with perceived need for fracture prevention medication if fractures were considered to have only trivial health consequences, and that conversely fractures perceived to have severe health consequences would not be associated with medication need if that person felt they were at minimal risk of experiencing the fracture. Therefore, we scaled the lowest score for both susceptibility to fracture and severity of fracture to equal zero, and created a variable called fracture susceptibility*severity as the interaction between the two.

Fracture knowledge regarding the health consequences of fractures was assessed with a 6 item scale that we developed for this study to assess knowledge regarding possible health consequences of fractures. *Medication use self-efficacy* was measured with 7 items selected from the validated scale of Resnick and colleagues,(209) assessing how confident patients felt they could execute medication use behavior in the context of their daily lives. *Depression* was assessed with three items assessing self-reported depressed mood in the recent or more distant past as well as current and/or past use of anti-depressant therapy. This was scored dichotomously as present if any of the three were endorsed, and as absent if all three items were not endorsed. *Medication cost burden* was assessed with one item.

Principle components analysis using orthogonal rotation for all items from the above seven scales showed that all items were associated with postulated factor with

loadings >0.4, and were not associated any other factor with a loading >0.3. Internal consistency reliability (Cronbach's alpha) was lowest for the depression and knowledge scales but was over 0.8 for all of the other scales, and highest for the patient-provider relationship quality (**table 2-7**).

A personal history of spine, hip, wrist, pelvis, or upper arm fracture was assessed by self-report, as was a history of spine or hip fracture in a first degree relative.

Control Variables – from medical record review

Medical record review was done for all 729 full respondents and also for all others (380) who were not deceased, had not actively refused participation, and who had been prescribed neither IV bisphosphonates nor teriparatide between January 1, 2006 and March 31, 2007. We postulated that those with prior bad experiences with medications may be more likely to attribute adverse medical events or symptoms to their fracture prevention therapy and stop taking it for this reason, and assessed this as the number of adverse drug reactions (ADR's) recorded in the medical record. Since the most common side effect leading to discontinuation of oral bisphosphonates is stomach upset, we postulated that a gastric acidity disorder such a gastro-esophageal reflux disease would predispose individuals to stop oral bisphosphonate therapy on account of perceived side effects. As a surrogate marker of gastric acidity disorder, we assessed whether or not a prescription of a proton pump inhibitor for more than one month between January 1, 2006 and March 31, 2007 had been recorded in the medical record. Smoking status, assessed at each Park Nicollet Clinic visit and entered into the medical record as a "vital sign", and oral glucocorticoid use for more than three months between January 1, 2006 and March 31, 2007 were also recorded.

If one or more bone density tests had been done, bone mineral density of the lumbar spine, total hip, femoral neck, and/or the forearm from the test done nearest in time to January 1, 2006 was recorded. We also recorded whether or not a lateral spine image was done with the bone mineral density test to document a prevalent vertebral fracture, and if it was, whether or not one or more prevalent vertebral fractures were documented by the physician interpreting the test.

Statistical Analysis

Individuals whose surveys were missing data one-half or more of the items making up any of the scales were excluded. The remainder of the missing data was filled in with statistical imputation, creating a univariate imputation model for each missing item using all other items (including those from other scales and demographic variables) as predictor variables. A posterior distribution for each missing variable was created from these models, and a value for each missing datum was randomly selected from these distributions and imputed into the dataset.

Continuous Variable Distributions

The summed raw scores for concerns about medication, the patient-provider relationship quality, and worst bone mineral density T-score were all normally distributed. The distribution of perceived need for medication was skewed, and the summed raw scores were squared to achieve a normal distribution. The distribution of perceived fracture susceptibility*severity was also skewed, but the raw scores to the 0.7 power were normally distributed and these transformed values were used in all statistical analyses.

Validation of Self-Reported Persistence and Non-Compliance (missed doses)

Validation of self-reported persistence and self-reported non-compliance (missed doses) was done in two ways. Pharmacy claims data for oral bisphosphonate use between the dates of January 1, 2006 and March 31, 2007 were available for that subset of study participants whose health insurer was HealthPartners (n=82), as Park Nicollet clinic had access to those claims for those patients designating Park Nicollet clinic as their health care provider. The Medication Possession Ratio (MPR) was calculated as the ratio of the number of days of medication available for use as prescribed between the first and last prescriptions divided by the total number of days between the first and last prescriptions. A dichotomous variable was created, with "non-compliance" defined as an MPR < 0.8, and "compliance" defined as an MPR ≥ 0.8. Agreement between overall non-persistence and self-reported non-compliance and compliance as defined by MPR was assessed using kappa statistics (**table 3-1**).

Non-persistence was also assessed by medical record review, and medical record non-persistence defined as documentation in the medication section of the medical record of an oral bisphosphonate being stopped and the passage of more than

one month before the same or another fracture prevention medication being prescribed. Agreement between overall non-persistence and medical record non-persistence was assessed using kappa statistics (**table 3-1**).

Single Equation Regression Models

Logistic regression models were run for the three non-persistence dependent variables; non-persistence for any reason, due to side effects, and for reasons other than side effects. Each model included the four medication attitude predictors; perceived need for fracture prevention medication, concerns about medications, medication use self-efficacy, and medication cost-burden. Initial models also included the following control covariates; age, sex, educational attainment, income level, bone mineral density level, personal history of clinical fracture, family history of fracture, prevalent vertebral fracture, smoking status, chronic oral glucocorticoid use, fracture knowledge, depression, and the patient-provider relationship quality. Control covariates were eliminated in a stepwise fashion if their association with all three dependent variables was at a p-value of >0.20. However, the final models included all covariates that were significantly associated with *any* of the non-persistence dependent variables, so that qualitative comparisons of the strength of associations between predictors and different types of non-persistence could be done.

For those still being prescribed an oral bisphosphonate medication, logistic regression models were also run with the same main predictors and control covariates. Control covariates were again eliminated in a stepwise fashion if their association with non-compliance was at a p-value of >0.20.

Multivariate Path Models

Because we postulated a direct association between concerns about medications and perceived need for fracture prevention medication, even a model restricted to the four main medication attitude predictors would include one predictor (concerns about medication) that would have an additional indirect effect on medication use behavior through its effect on perceived necessity for fracture prevention medication. Single regression equation models will only capture the direct association between medication concerns and medication use behavior, and hence will underestimate the full effect of medication concerns. Therefore, figure 1 was also

estimated as a multivariate path model to estimate the total effect of medication concerns on medication use behavior. The multivariate models consisted of six simultaneous regression equations; three probit regressions with medication use behavior, medication use self-efficacy, and perceived medication cost burden as the dependent variables, and three OLS regressions with perceived necessity for medication, perceived fracture severity-susceptibility, and concerns about medications as the dependent variables.

Instrumental Variables Analysis

The multivariate path models are subject to bias if the error terms of the included regression equations are correlated. To evaluate bias in the multivariate models from such error correlations, an instrumental variables regression utilizing the *ivprobit* command of Stata 9.1 was run using demographic variables, objective indicators of fracture risk, fracture knowledge, depression, and the patient-provider relationship quality as instruments for perceived need for medication and concerns about medications. Since we are also postulating a direct effect of concerns about medications on perceived need for medication, two sets of analyses were done, the first set instrumenting only for perceived need for medication (using concerns about medication as one of the instruments), and a second set instrumenting for both perceived need for medication and concerns about medications. These models were first estimated in one step with a maximum likelihood estimator, but if convergence could not be achieved, then a two-step estimator(269) was used. Wald tests were done to assess if the error terms of these regressions were correlated.

Results

Surveys were mailed to all 1179 individuals within the Park Nicollet care system who appeared to met all inclusion and exclusion criteria, but medical record review subsequently showed that 20 had received either intravenous bisphosphonate medication or subcutaneous teriparatide during the period January 1, 2006 through March 31, 2007, were deceased, had never been prescribed an oral bisphosphonate, or had documentation of dementia. Hence the denominator to determine our response rate was 1,159 eligible participants, and among these 794 returned surveys, 4 surveys were returned as undeliverable, and 50 recipients called back actively refusing

participation. Sixty-five respondents were excluded because more than one-half of the items for one or more of the scales measuring predictor variables were not answered. The final response rate was 729 of 1159, or 62.9%. Among these 729 respondents, 59% sent their survey back by July 31, and 97% had returned their survey by August 31, 2007. Complete data was present for 510 (70%) and for the remaining 219 survey respondents a mean 1.26 items (of a total of 57) per participant had to be imputed.

The characteristics of the 729 respondents with useable survey data and 380 non-respondents who did not actively refuse study participation are shown **table 3-2**. Respondents were nearly two years older, were slightly more likely to have an active, current prescription for an oral bisphosphonate recorded in the medical record at the time the survey was mailed, had more adverse drug reactions in the medical record than non-respondents, and slightly more were current smokers. Non-respondents and respondents were no different with respect to sex, weight, bone mineral density, documentation of prevalent vertebral fracture, or use of oral glucocorticoids or proton pump inhibitors. Among respondents, 24.4% had less than a high school education, 23.9% were college graduates, nearly one-third had a personal history of fracture, and one-third had a family history of spine or hip fracture in a first degree relative.

Single Regression Equations

Overall self-reported non-persistence was strongly associated with perceived need for fracture prevention medication, and more modestly with concerns about medications, medication use self-efficacy, two or more adverse drug reactions, use of a proton pump inhibitor, current cigarette smoking, and younger age (**table 3-3**). Medication use self-efficacy was modestly inversely associated with overall non-persistence. Self-reported non-persistence due to side effects was also associated strongly with perceived need for medication and 2 or more adverse drug reactions, modestly with medication concerns and proton pump inhibitor use, but not with medication use self-efficacy or perceived medication cost burden.

In contrast, self-reported non-persistence for reasons other than side effects was not associated with medication concerns, the number of adverse drug reactions, or proton pump inhibitor use. However, there was a strong association with perceived need for fracture prevention medication and the highest level of perceived cost burden, and a moderate inverse association with medication use self-efficacy.

Among those reporting that they were currently being prescribed an oral bisphosphonate medication at the time the survey was mailed, non-compliance (missed doses) was modestly positively associated with medications concerns and strongly negatively associated with medication use self-efficacy (**table 3-4**). Non-compliance was also significantly negatively associated with age, but no clear association was present between non-compliance and perceived need for fracture prevention medication, medication cost burden, use of a proton pump inhibitor, or the number of adverse drug reactions in the medical record.

Objective measures of fracture risk (bone mineral density, prevalent vertebral fracture, family history of fracture, and personal history of fracture) and the provider-patient relationship quality were not associated with any aspect of self-reported medication use behavior independent of other predictors.

Multivariate Path Models

The standardized effects for each of the four primary medication attitudes variables on each of the four dependent medication use behavior variables are shown in **figure 3-1**. Concerns about medication were modestly but significantly associated with perceived need for medication, and concerns about medication had significant indirect effects through need for medication on overall non-persistence, non-persistence due to side effects, and non-persistence due to other reasons. These indirect effects represent, respectively, 31.8%, 17.8%, and 50.8% of the total effects of concerns about medications on overall non-persistence, non-persistence due to side effects, and non-persistence for other reasons. Among the subset on an oral bisphosphonate medication at the time of the survey, nearly all of the effects of medication concerns on non-compliance (missed doses) are direct.

A one standard deviation (SD) change in perceived need for medication (from the mean to 1 SD above the mean) would be predicted to cut the proportion of those self-reporting non-persistence due to side effects, for other reasons, or for any reason by one-third (**table 3-5**). A one SD decrease of medication concerns below the mean would be predicted to cut overall self-reported non-persistence, non-persistence due to side effects, and the proportion missing doses by about one fifth to one quarter. Achieving high medication use self-efficacy would be predicted to reduce the proportion of those missing doses of fracture prevention medication by one-third.

Otherwise, changes in medication use self-efficacy and perceived medication cost burden have only slight effects on self-reported medication use behavior.

Instrumental Variables Analysis

For each of the four medication use behavior dependent variables, instrumental variables analyses, estimated with a maximum likelihood estimator) and using instruments only for perceived need for medication (using concerns about medications as one of the instruments), showed no evidence of error correlations between the regressions of perceived need for medication and of medication use behavior (**table 3-6**). In this instance, instruments for perceived need postulated to be uncorrelated with any of the medication use behavior dependent variables (independent of other predictors) were income, education level, sex, bone mineral density, family history of fracture, personal history of fracture, prevalent vertebral fracture, depression, and fracture knowledge.

Analyses instrumenting for both perceived need for medication and concerns about medications similarly showed no evidence of error correlations between the error terms of either of these two endogenous predictor and any of the four medication use behavior dependent variables (**table 3-7**). In this instance, models using a one-step maximum likelihood estimator would not converge, and these models were estimated using a two-step estimator. Instruments for both perceived need for medication and concerns about medication postulated to be uncorrelated with any of the medication use behavior dependent variables (independent of other predictors) were income, education level, sex, bone mineral density, family history of fracture, personal history of fracture, prevalent vertebral fracture, depression, fracture knowledge, and number of medication doses each day.

Discussion

Non-persistence and non-compliance with medication to prevent osteoporotic fracture has been shown in a large number of descriptive studies done with pharmacy claims to be common among those prescribed oral bisphosphonate therapy.(28, 29, 34, 38, 44) Those who are non-persistent and/or non-compliant are more likely to suffer fractures than those who are persistent and compliant with oral bisphosphonate medication.(33, 34, 59, 61, 63, 65)

In this retrospective cross-sectional survey and medical record review study, perceived need for medication, concerns about the long-term safety of and dependence upon medication, and medication use self-efficacy were significantly associated with overall non-persistence. The associations of perceived need for medication and medications concerns with medication persistence were quite consistent with studies of Horne and colleagues, who have documented these associations in patient populations with other chronic diseases.

Certain variables were more strongly associated with non-persistence due to side effects than with non-persistence due to other reasons, and vice versa. Medications concerns, number of adverse drug reactions, and use of a proton pump inhibitor were all associated with non-persistence due to side effects but not with non-persistence for other reasons. A medication side effect requires the occurrence of both an adverse event *and* attribution of causality for that event to the medication. We suspect that those with concerns about the long-term safety of medications and/or prior bad experiences with medications may be quicker to attribute the cause of an adverse event to one or more of their current medications. The association between medication concerns and non-persistence due to side effects could conceivably be due to reverse causality (side effects causing medication concerns), but we believe this is unlikely given that medication concern was not associated with the number of adverse drug reactions in the medical record. We believe that the use of a proton pump is associated with non-persistence due to side effects because PPI use is a marker for gastric acidity disorder and tendency to experience adverse upper gastrointestinal events, and such events are the most likely side effects associated with oral bisphosphonate drugs. Since we did not directly assess the experience of adverse effects and perceived cause of those events, further research will be required to confirm these hypotheses.

Conversely, non-persistence for reasons other than side effects was associated with medication use self-efficacy and the highest level of perceived cost burden, but not with medication concerns, number of ADR's, and PPI use. While others have not found perceived cost burden to be associated specifically with medication use to prevent fractures, those other studies have not specifically separated non-persistence due to side effects from non-persistence due to other reasons.

Perceived need for fracture prevention medication turned out to have the greatest impact on overall non-persistence. While the overall effect of concerns about

medications appeared to be more modest, a significant proportion of the effects of medication concerns on non-persistence was indirect through perceived need for fracture prevention medication. Concerns about medication have greater effects on self-reported medication non-persistence than indicated by single equation regression models, and in the case of non-persistence due to side effects, the magnitude of its effect is as great as that of perceived need for fracture prevention medication.

Among those who report they have a current prescription for an oral bisphosphonate, non-compliance to oral bisphosphonate medication (conceptualized as missing doses) was as expected particularly and strongly associated with medication use self-efficacy, and also modestly with medication concerns. An important component of concerns about medications as conceptualized in this study is concern about *dependence* on medication, and a belief that medications should be stopped for while every now and then. We hypothesize, based on these results, that avoiding medication every now and then reduces these patient's fears of dependence upon and long-term harm from chronic medications. Further research will be required to confirm this hypothesis. If this hypothesis is correct, it would imply that even among individuals who do not deliberately stop a prescribed medication, doses may be missed for both intentional reasons and/or unintentionally.

In contrast, we found no association between non-compliance and perceived need for fracture prevention medication. It appears that if a person has sufficient perceived need for medication not to stop it altogether, that then other factors are much more important in determining whether or not they miss doses. Among the 607 participants who reported being prescribed an oral bisphosphonate medication at the time of the survey, 21.4% and 24.7%, respectively, were nonetheless in the lowest and next to lowest quartiles of need for fracture prevention medication, and hence lack of variation in the predictor variable cannot account for this negative result.

Although we did not demonstrate any direct association of objective measures of fracture risk, fracture knowledge, and the patient-provider relationship quality with any formulation of medication use behavior independent of the other predictors included in our models, it should noted that these variables may still have important effects on medication use behavior through medication attitudes such as perceived need for fracture prevention medication and concerns about medications. These

indirect associations are beyond the scope of this paper but will be addressed in subsequent publications.

Our results parallel the associations of compliance with medication to treat other chronic diseases with perceived need for medication and medication concerns that Horne and colleagues have reported.(143, 145-147, 266, 270) With respect to concerns about medications, our results are consistent with those of Carr and colleagues,(265) and McHorney and colleagues(41) who noted a similar association between concerns about the long-term safety of and dependence upon medication and self-reported use of fracture prevention medication. The results of this study are also consistent with those of McHorney et. al.(41) and Cline and colleagues(58) who found that strong beliefs in the efficacy of fracture prevention medication to be strongly associated with compliance to fracture prevention medication as measured by pharmacy refill records and self-report.

Perceived efficacy of fracture prevention medication is not synonymous with perceived need for fracture prevention medication. One could logically believe that a medication that effectively prevents fractures is nonetheless not needed if one believes that one is not susceptible to those fractures, that fractures are of trivial consequence, or that the medication also may cause significant harm to one's health. Nonetheless, we believe that belief in the efficacy of a fracture prevention medication is a necessary, albeit insufficient, condition to consider a fracture prevention medication necessary to maintain one's health. While several survey studies have suggested that side effects is the most important reason for these to be discontinued,(41, 50, 54, 57, 265, 271) other qualitative research studies performed with focus groups and discrete choice experiments have shown that beyond the experience of short-term side effects, patients express significantly greater willingness and intent to adhere to medication they perceive to be effective and safe with long-term use.(136, 272-284)

This study adds significantly to the existing medication compliance literature several important ways. While three other studies have used multivariable regression models to assess the associations of medication attitudes and beliefs with fracture prevention medication compliance adjusting for other predictors,(41, 58, 265) only one prior study used multivariate path models so that indirect effects of predictors on medication use behavior through other predictors can be assessed.(145) This prior study, however, did not report use of instrumental variables or other analyses to

assess their multivariate path model for bias from regression error correlations. Second, ours is the first to conceptualize perceived need for medication as an attitudinal predictor of and to assess the utility of the medication necessity-concerns framework to explain use of fracture prevention medication. Third, in contrast to other studies of the medication necessity-concerns framework as an explanatory model for medication use behavior in chronic diseases other than osteoporosis, this is the first to demonstrate that some of the effect of concerns about medications is through perceived need for medication.

Fourth, ours is the only study to specifically assess predictors of non-persistence due to side effects in comparison to predictors of non-persistence for reasons other than side effects. Other studies have considered side effects to be a predictor in and of itself for discontinuation of medication. However, a side effect can be conceptualized as the serial combination of an adverse event followed by a causal attribution of that event to one or more of the medications currently being used. Investigation of why side effects are perceived and why those perceptions lead to medication non-compliance may yield clues as to why and how patients make causal inferences that a particular drug is causing an adverse event. While our study gives some initial clues as to what factors may influence this process, clearly further research is needed in this area.

Fifth, while other studies have investigated barriers such as cost or difficulty with dosing instructions as predictors of medication non-compliance, ours is the only study to use medication use self-efficacy as a predictor in multivariable models of fracture prevention medication. While difficulty with dosing instructions for a specific medication is highly likely to be correlated with medication use self-efficacy, we believe medication use self-efficacy to be a more generalized attitude. However, further research is required to determine if medication use self-efficacy is associated with non-compliance with medications used to treat other chronic conditions.

Our study has other important strengths. The response rate of this study (63%) is equivalent to or better than that reported in most other survey studies of fracture prevention medication compliance. Our use of a multivariate path model to assess indirect effects of predictors on medication use behavior used instrumental variables analysis to look for bias from regression error term correlations, to yield robust direct and indirect estimates of these effects. Compared to other studies of predictors of

fracture prevention medication use behavior, we were better able to compare survey respondents to non-respondents on account of having access to the medical record.(41, 58)

The overall effect of these variables is modest, and the full path models estimated that 22%, 18%, 23%, and 23%, respectively, of the variances of overall non-persistence, non-persistence due to side effects, non-persistence for other reasons, and non-compliance were explained by these models. The explanatory power of these models is slightly lower than other studies of the necessity –concerns framework and medication use behavior where non-persistence and non-compliance were assessed by self-report and modeled as continuous variables.(143, 145) The area under the ROC curves for our single equation models predicting non-persistence or non-compliance (0.71 to 0.74) were slightly lower compared to the only study of the association of compliance with fracture prevention medication as assessed by pharmacy claims and medication attitudes (ROC curve area 0.82).(41) We suspect that we lost some explanatory power of medication use behavior by using self-report rather than pharmacy claims to assess medication use behavior, and by the necessity to model self-reported medication use behavior as dichotomous rather than continuous variables. However, the effect of this modest loss of precision would be to bias our associations between medication attitudes and medication use behavior toward the null.

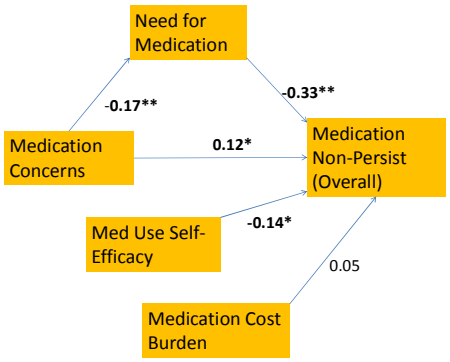
There are other important limitations to our study. Although our response rate is reasonable, a larger proportion of non-respondents did not have a current prescription for oral bisphosphonate therapy in the medical record, and therefore is it likely that a higher proportion of survey non-respondents were non-persistent with fracture prevention medication and that our respondent subset is not fully representative of the population of patients prescribed oral bisphosphonate medications. Second, self-report was used to assess non-persistence and non-compliance, as we did not have access to pharmacy claims for our full study sample. However, we were able to assess the correspondence between our self-report measures of medication use behaviors and pharmacy claims in a small subset of our sample, and between self-reported non-persistence and medical record documentation of fracture prevention medication discontinuation. While these correlations were only modest, they are consistent with other studies.(239, 241, 245, 247, 248, 285) The cross-sectional nature of our study

means that we cannot rule out reverse causality as an explanation for some of our findings. For example, it is conceivable that some patients concluded that they did not need fracture prevention medication if they stopped the medication and then did not experience any fractures. If the association between perceived need for medication and non-persistence is in part due to reverse causality, the apparent strength of the direct effect of perceived need for fracture prevention medication on non-persistence may be exaggerated. However, the similarity between the parameter estimates for perceived need for medication when it is modeled as an exogenous predictor and when it is instrumented would suggest that this is not a serious source of bias. Finally, our study population included patients from only one large multi-speciality clinic and was overwhelmingly white and female, thereby limiting the generalizability of the results of this study.

In conclusion, medication non-persistence due to side effects with oral bisphosphonate medication to prevent fractures appears to be negatively associated with perceived need for medication and positively associated with prior adverse experiences with medications, concerns about the long-term safety of and dependence upon medications, and use of proton pump inhibitors. Non-persistence for reasons other than side effects with oral bisphosphonate medication to prevent fractures appears to be negatively associated with perceived need for fracture prevention medication, medication use self-efficacy, and positively with the highest level of perceived cost burden and with younger age. In contrast, non-compliance (missing doses) appears to be associated primarily with medication use self-efficacy, concerns about the long-term safety of and dependence upon fracture prevention medication, and younger age. Interventions to improve fracture prevention medication compliance that elicit and address patients' concerns about medication safety, dependence and cost, their medication use self-efficacy, and also whether or not patient's perceived need for fracture prevention medication is based on a realistic appraisal the health consequences of not taking medication may improve medication use behavior.

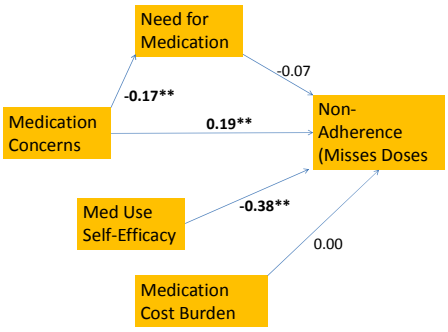
Figure 3-1: Effects of Medication Attitudes on Medication Use Behavior

Panel A – Overall Non-Persistence



Model Fit Statistics: Chi^2 45.8, p-value=0.24
value=0.20
CFI = 0.98, RMSEA = 0.015

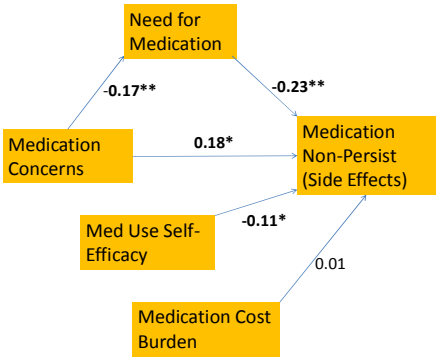
Panel B – Non-Compliance (Missed Doses)



Model Fit Statistics: Chi^2 47.0, p-

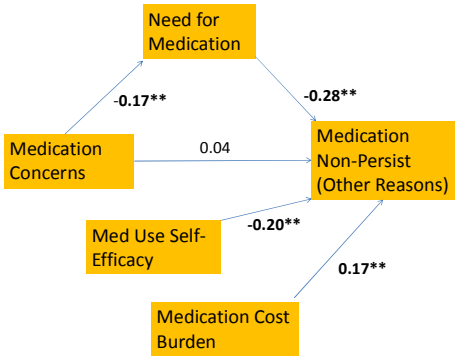
CFI = 0.97, RMSEA = 0.016

Panel C – Non-Persistence (Side Effects)



Model Fit Statistics: Chi^2 45.8, p-value=0.21
value=0.24
CFI = 0.97, RMSEA = 0.016

Panel D- Non-Persistence (Other Reasons)



Model Fit Statistics: Chi^2 45.8, p-

CFI = 0.97, RMSEA = 0.015

*Effect significant at p-value <0.05
**Effect significant at p=value <0.01

Table 3-1: Agreement Between Self-Reported Overall Non-Persistence and (Among Persisters) Non-Compliance and Other Measures of Oral Bisphosphonate Non-Compliance)

Objective Measure of Non-Compliance	Self-Reported Non-Persistence		Self-Reported One or More Missed Doses	
	Number of Patients	Kappa (Standard Error)	Number of Patients	Kappa (Standard Error)
Medication Possession Ratio	82	0.28 (0.11)	69	0.40 (0.11)
Medical Record Documentation of Non-Persistence	729	0.47 (0.04)	N/A*	N/A*

*Not applicable

Table 3-2: Characteristics of Study Survey Responders and Non-Responders

Variable	Final Responder (n=729)	Non-Final Responder (n=380)	P-value
Age, age (SD)	66.4 (10.1)	64.6 (10.8)	**<0.01***
Sex: Women Men	Women: 681 (93.4%) Men: 48 (6.6%)	Women: 356 (93.7%) Men: 24 (6.3%)	0.86**
Body Weight (Medical Record), lbs (SD)	148.7 (30.8)	147.7 (31.5)	0.61*
Still On Fracture Oral Prevention Med (Medical Record):	Yes: 626 (85.9%) No: 103 (14.1%)	Yes: 299 (78.7%) No: 81 (21.3%)	**<0.01****
Oral glucocorticoid Use (Medical Record)	Yes: 66 (9.0%) No: 663 (91.0%)	Yes: 41 (10.8%) No: 338 (89.2%)	0.35**
Proton Pump Inhibitor Use (Medical Record)	Yes: 189 (25.9%) No: 540 (74.1%)	Yes: 92 (24.2%) No: 288 (75.8%)	0.53**
Number of ADR's (Medical Record)	0: 324 (44.4%) 1: 281 (38.5%) ≥ 2: 124 (17.1%)	0: 163 (42.9%) 1: 94 (24.7%) ≥ 2: 123 (32.4%)	**<0.01****
Smoking Status (Medical Record)	Current: 62 (8.5%) Past: 258 (35.5%) Never: 406 (55.9%)	Current: 48 (12.9%) Past: 119 (31.9%) Never: 206 (55.2%)	0.06**
Worst Bone Density T-score (SD)	-2.64 (0.65)	-2.67 (0.74)	0.42*
Prevalent Vertebral Fracture on VFA	No: 180 (24.7%) Unknown: 490 (67.2%) Yes: 59 (8.1%)	No: 86 (26.5%) Unknown: 209 (64.5%) Yes: 29 (8.9%)	0.69**
Educational Status Some High School High School Grad Some College College Grad	 178 (24.4%) 233 (32.0%) 144 (19.7%) 174 (23.9%)	Not Available	
Income Per Year <$30,000 30 to $59,000 60 to $89,000 ≥ $90,000	 181 (24.8%) 203 (27.8%) 140 (19.2%) 205 (28.1%)	Not Available	
Personal History of Hip, Spine, Wrist, Humerus, or Pelvis Fracture	Yes: 33.7% No: 66.3%	Not Available	
Family History of Hip or Spine Fracture	Yes: 28.5% No: 71.5%	Not Available	

***Student t-test** **Chi-square

Table 3-3: Predictors of Non-Persistence Due to Side Effects and for Reasons Other than Side Effects^

Predictor	Non-Persistence Overall* OR (95% C.I.)	Non-Persistence Due to Side Effects** OR (95% C.I.)	Non-Persistence For Other Reasons*** OR (95% C.I.)
Perceived Need for Medication (squared)	***0.53 (0.44 – 0.64)***	***0.60 (0.48 – 0.75)***	***0.61 (0.49 – 0.77***
Medication Concerns (per SD increase)	1.19 (1.00 – 1.43)	***1.24 (1.01 – 1.53)***	1.09 (0.88 – 1.35)
Medication Use Self-Efficacy	***0.67 (0.48 – 0.94)***	0.79 (0.52 – 1.18)	***0.61 (0.40 – 0.95)***
Med Cost Burden			
Quintile 2 vs. 1	0.76 (0.46 – 1.24)	0.84 (0.46 – 1.51)	1.26 (0.64 – 2.46)
Quintile 3 vs. 1	0.57 (0.31 – 1.03)	0.80 (0.40 – 1.60)	1.01 (0.45 – 2.25)
Quintile 4 vs. 1	0.67 (0.39 – 1.17)	0.92 (0.49 – 1.73)	1.54 (0.75 – 3.13)
Quintile 5 vs. 1	1.25 (0.70 – 2.21)	0.70 (0.35 – 1.41)	***3.36 (1.66 – 6.79)***
Number Adverse Drug Reactions			
Tertile 2 vs. 1	1.15 (0.79 – 1.67)	***1.70 (1.08 – 2.69)***	0.86 (0.54 – 1.38)
Tertile 3 vs. 1	***1.93 (1.18 – 3.13)***	***2.78 (1.60 – 4.85)***	1.75 (1.00 – 3.07)
Use of Proton Pump Inhibitor	***1.66 (1.13 – 2.43)***	***1.60 (1.04 – 2.45)***	0.94 (0.59 – 1.51)
Age (per 10 year increase)	***0.80 (0.67 – 0.95)***	0.96 (0.78 – 1.18)	***0.72 (0.59 – 0.90)***
Smoking Status:			
Past vs. Never	1.30 (0.90 – 1.86)	1.18 (0.77 – 1.79)	1.16 (0.75 – 1.82)
Current vs. Never	***2.22 (1.22 – 4.05)***	1.37 (0.67 – 2.77)	***2.26 (1.16 – 4.37)***

^Parameter estimates in ***bold*** are statistically significant at $p < 0.05$ level

*Area under ROC curve 0.72 (95% C.I. 0.69 – 0.76)

**Area under ROC curve 0.71 (95% C.I. 0.67 – 0.76)

***Area under ROC curve 0.74 (95% C.I. 0.69 – 0.78)

Table 3-4: Predictors of Non-Compliance (One or More Missed Doses Over the Past Month) Among Those Persisting With Oral Bisphosphonate Therapy^

Predictor	Non-Compliance* (Yes vs. No) OR (95% C.I.)
Perceived Need for Medication	0.86 (0.71 – 1.06)
Medication Concerns (per SD increase)	***1.26 (1.04 – 1.52)***
Medication Use Self-Efficacy	***0.42 (0.29 – 0.61)***
Medication Cost Burden	
Quintile 2 vs. 1	0.75 (0.43 – 1.33)
Quintile 3 vs. 1	1.29 (0.68 – 1.43)
Quintile 4 vs. 1	0.98 (0.54 – 1.80)
Quintile 5 vs. 1	1.05 (0.55 – 2.02)
Use of Proton Pump Inhibitor	1.02 (0.68 – 1.56)
Number Adverse Drug Reactions	
Tertile 2 vs. 1	1.18 (0.79 – 1.76)
Tertile 3 vs. 1	1.19 (0.70 – 2.04)
Age (per 10 year increase)	***0.60 (0.49 – 0.73)***

^Parameter estimates in ***bold*** are statistically significant at $p < 0.05$ level

*Area under ROC curve 0.70 (95% C.I. 0.66 – 0.74)

Table 3-5: Changes of Predicted Proportions Non-Persistence of Missed Doses With Changes of Medication Attitude Predictors

Predicted Outcome	Predictor							
	Perceived Need*		Concerns about Medications*		Medication Use Self-Efficacy**		Perceived Medication Cost Burden***	
Level of Predictor	Mean	+1 SD	Mean	-1 SD	Low	High	4th Quintile	2nd Quintile
Overall Non-Persistence	34.2%	22.9%	34.2%	27.9%	40.3%	34.9%	32.4%	30.7%
Non-Persistence (Side Effects)	18.9%	13.3%	18.9%	13.6%	22.0%	18.9%	21.2%	20.8%
Non-Persistence (Other Reasons)	17.8%	11.6%	17.8%	15.6%	22.8%	17.1%	18.5%	14.4%
Non-Compliance (Missed Doses)	34.6%	32.1%	34.6%	27.5%	44.9%	30.6%	35.3%	34.9%

*All other predictors set to mean values

**All other predictors set to values associated with low self-efficacy

***All other predictors set to values associated with the 4th quintile of perceived medication cost burden

Table 3-6: Parameter Estimates for Predictors of Medication Use Behavior When Perceived Need is Exogenous and When Perceived Need is Instrumented

Medication Use Behavior Dependent Variable	Perceived Need Exogenous* (95% C.I.)	Perceived Need Instrumented* (95% C.I.)	Wald Test Chi-square^
Overall Non-Persistence	-0.37 (-0.49 to -0.26)	-0.39 (-0.81 to 0.02)	0.01 (p-value = 0.91)
Non-Persistence (Side Effects)	-0.25 (-0.37 to -0.12)	-0.18 (-0.68 to 0.32)	0.07 (p-value = 0.79)
Non-Persistence (Other Reasons)	-0.29 (-0.42 to -0.16)	-0.49 (-0.93 to -0.05)	0.73 (p-value = 0.39)
Non-Compliance (Missed Doses)	-0.07 (-0.19 to 0.05)	0.19 (-0.37 to 0.75)	0.81 (p-value = 0.37)

^Wald chi-square test is for significance for correlation between the error terms of the individual regressions within the multivariate model

*Parameter estimates are standardized to standard deviation of perceived need for medication squared

Table 3-7: Parameter Estimates for Predictors of Medication Use Behavior When Perceived Need and Medication Concerns are Exogenous and When Perceived Need and Medication Concerns are Instrumented

Medication Use Behavior	Perceived Need for Medication*		Concerns about Medication*		Wald Test Chi^2 (p-value)^
	Exogenous (95% C.I.)	Instrumented (95% C.I.)	Exogenous (95% C.I.)	Instrumented (95% C.I.)	
Overall Non-Persistence	-0.37 (-0.49 to -0.26)	-0.43 (-0.87 to 0.01)	0.11 (0.00 to 0.22)	0.03 (-0.34 to 0.39)	0.24 (0.89)
Non-Persistence (Side Effects)	-0.25 (-0.37 to -0.12)	-0.32 (-0.82 to 0.18)	0.13 (0.01 to 0.26)	-0.09 (-0.50 to 0.33)	1.60 (0.45)
Non-Persistence (Other Reasons)	-0.29 (-0.42 to -0.16)	-0.53 (-1.04 to -0.02)	0.05 (-0.08 to 0.17)	-0.11 (-0.54 to 0.31)	1.02 (0.60)
Non-Compliance (Missed Doses)	-0.07 (-0.19 to 0.05)	0.07 (-0.43 to 0.57)	0.15 (0.03 to 0.27)	0.13 (-0.26 to 0.52)	0.60 (0.74)

^Wald chi-square test is for significance for correlation between the error terms of the individual regression equations within the multivariate model

*Parameter estimates are standardized to standard deviation of perceived need for medication squared

Chapter 4:
Predictors of Patient Perceived Need for Medication to Prevent Fracture

Abstract

Background: Persistence with and compliance to medications to prevent fractures among patients with osteoporosis is suboptimal. Perceived need for medication is postulated to be an important predictor of medication use behavior, consistent with discrete choices made by patients on the basis of perceived utility and costs of alternative behavioral choices. However, no study to date has investigated what factors predict the degree to which a patient will perceive a need to take a medication to prevent adverse health events from fractures in the future. Specifically, among those with osteoporosis, no study has investigated the degree to which objective indicators of fracture risk, and independent of these the association of the patient-provider relationship quality, determine a patient's perceived need for medication to prevent future fractures.

Objective: To estimate the association of perceived need for fracture prevention medication within the context of a conceptual path model with the following postulated predictor variables; knowledge of fractures, bone mineral density, family history of fractures, personal history of fractures, prevalent vertebral fracture documented on lateral spine imaging, perceived susceptibility to and health consequences of fractures, concerns about the long-term risks of and dependence upon medications, and the quality of the patient-provider relationship quality.

Methods: A cross-sectional survey and medical record review was carried out among 1,159 individuals prescribed an oral bisphosphonate medication between January 1 2006 and March 31 2007. Bone mineral density and prevalent vertebral fracture status were assessed by medical record review. All other variables were assessed by self-report scales or single survey items. A multivariate path model was fit to estimate the conceptual model of predictors of perceived need for medication. Instrumental variables regression models were used to assess bias from the inclusion of endogenous predictors in the multivariate model.

Results: Perceived susceptibility to and severity of fractures and the patient-provider relationship quality were moderately and significantly associated with perceived need for fracture prevention medication. Concerns about the long-term safety of and dependence upon medications was mildly but significantly negatively associated with perceived medication need. Bone mineral density, personal history of fracture, and family history of fracture were only weakly associated with perceived medication need.

Independent of all of these other predictors, those with one or more prevalent vertebral fractures on lateral spine imaging were significantly more likely to perceive need for fracture prevention medication.

Conclusion: The patient-provider relationship quality has a modest effect on perceived need for fracture prevention medication. However, several objective indicators of fracture risk are only weakly associated with perceived for fracture prevention medication, suggesting that providers may not be leveraging the trust that the patient's have in them to improve patient understanding of their fracture risk. Documenting one or more prevalent vertebral fractures on lateral spine imaging may influence patients perception of their need for fracture prevention medication and has the potential to positively influence persistence with fracture prevention medications.

Introduction

Fractures related to osteoporosis are an increasing cause of morbidity in the population, and in the case of hip fractures and possibly vertebral fractures, a cause of mortality as well. At age 60, men and women, respectively, have a 25% and a 44% chance of having a fracture related to osteoporosis in their remaining lifetimes.(259) Several medications have been shown to reduce the risk of fractures related to osteoporosis, beyond what non-medicinal measures such as optimizing vitamin D and calcium intake can achieve. The oral bisphosphonates are the most common type of medication used to preserve or improve bone strength, and reduce fractures by 30 to 50%.(260, 264, 286) However, numerous descriptive studies have shown that within 1 to 2 years of being prescribed an oral bisphosphonate medication, only 32 to 68% are still taking it.(28, 29) Generally, treatment courses of at least 3 to 5 years are recommended with oral bisphosphonate therapy.(287) This pattern of non-persistence has also been demonstrated in studies of oral medication used to prevent adverse health events associated with other chronic conditions such as hypertension,(24, 25, 288, 289) hyperlipidemia,(26, 27) and asthma.(290) Non-compliance with fracture prevention medication is in turn associated with higher incidence of fractures and health care costs.(34, 59, 60, 63)

Perceived need for medication has been shown to be a significant predictor of compliance with medication to treat a variety of chronic conditions,(143, 145-147, 266, 275, 291, 292) and may be a necessary but insufficient condition for medication compliance.(292) In turn, social cognition models such as the Health Belief Model(90, 92) and the Self-Regulatory Model(93) predict that perceived need for medication to prevent adverse future events such as fractures is, in turn, associated with perceived susceptibility to the target event, the perceived severity (health consequences) of the target event, the perceived efficacy of the drug, but also the perceived risks of the intervention. However, no studies to date have specifically examined how strongly these predictors are associated with perceived necessity for medication to prevent adverse future health events, including fractures. Moreover, no study to date has assessed the congruence of medication necessity beliefs and perceived susceptibility to the target condition with patients' actual risks of experiencing the target condition and the actual health consequences of that condition.

The primary objective of this analysis was to estimate the associations of perceived need for fracture prevention medication with perceived susceptibility to and severity of fractures, concerns regarding the long-term safety of and dependence upon medications, the quality of the patient-provider relationship quality and with objective indicators of fracture risk (bone mineral density, personal and family history of fractures, prevalent vertebral fracture on lateral spine imaging, cigarette smoking, and oral chronic glucocorticoid use). Our secondary objectives were to estimate the associations of perceived susceptibility to and severity of fractures with objective indicators of fracture risk, knowledge about fractures, and the patient-provider relationship quality.

Methods

This study was reviewed and approved by the Institutional Review Boards of both Park Nicollet Heath Services and the University of Minnesota.

Data

This dataset is from a survey and medical record review of patients given one or more prescriptions for oral bisphosphonate therapy at Park Nicollet Clinic between the dates of January 1, 2006 and March 31, 2007. Candidate participants were those age 21 to 84 with one or more prescriptions for a bisphosphonate medication in the electronic medication record in this time period, who had had a clinic visit within 6 months of the mailing date of the survey (to assure they were still receiving care at Park Nicollet Clinic), and did not have a diagnosis of dementia. Candidates for participation also had to have signed the Park Nicollet general consent form (given to all patients at time of registration as a clinic patient and updated once per year) allowing their medical records to be used for research purposes. We subsequently also excluded those who were prescribed intravenous bisphosphonates or subcutaneous teriparatide between January 1, 2006 and March 31, 2007, so that all questions regarding fracture prevention medication use would be unequivocally interpreted as regarding oral fracture prevention medications.

Potential study participants were mailed the survey during the week of July 16 through 20, 2007. Those who had not returned the survey within two weeks were mailed a reminder postcard. Those who had still not returned the survey or called in to actively refuse participation were mailed a second survey one month later. Among the

subset of survey respondents, 59% sent their survey back by July 31, and 97% had returned their survey by August 31, 2007.

Where possible, scales to measure these constructs were derived from previously validated scales, but for some constructs we were unable to find any appropriate measures and hence developed new scales to measure these. The unidimensionality of these scales was assessed using principle components analysis of all scale items together, and also from principle components analyses of each scale separately. A ratio of the first to second eigenvalue of greater than 3.0 was considered to be strong evidence of unidimensionality for each scale.

Conceptual Framework

The primary predictors of patient perceived need for fracture prevention medication were postulated to be perceived susceptibility to and severity (health consequences) of fractures, concerns about long-term safety of and dependence upon medications, and the quality of the patient-provider relationship quality (**figure 4-1**). We postulated that objective indicators of fracture risk (BMD, personal and family history of fracture, and prevalent radiographic vertebral fracture on spine imaging) would influence perceived need for fracture prevention medication primarily through perceived susceptibility to and severity of fractures, but that a direct effect on perceived need for fracture prevention medication might also be present due to imperfect measurement of perceived susceptibility to and severity of fractures with survey instruments. We also postulated a direct effect of concerns about the long-term safety of and dependence upon medication on perceived necessity for medication, since concerns that medications in the long-run may be injurious to health logically might lead a person to conclude that their health is *not* facilitated by use of a medication even if they are at high risk of the target condition and believe that the medication has efficacy.

The quality of the patient-provider relationship quality was postulated to have a direct effect on perceived need for medication, but to also to have a negative association with medication concerns and therefore to also have an indirect effect on perceived need for medication. We also postulated that knowledge about fractures would be associated with perceived susceptibility to and severity (health consequences) of spine and hip fractures should they personally experience

them.(293) We also postulated a direct effect of the patient-provider relationship quality on the perceived susceptibility to and severity of fractures.

Measurement of Variables – from survey items

Perceived necessity of fracture prevention medication was assessed by seven item scale, adapted from the validated medication necessity scale of Horne and colleagues.(142) Two items from the original scale were removed because they appeared to be inappropriate for those with completely asymptomatic conditions, and four additional items added to improve its internal consistency reliability. Items assessed both the patients' beliefs in the effectiveness of their medication to reduce their fracture risk and their perceived need for the medication to preserve their overall health. These sets of items could not be separated into separate domains with factor analysis and principal components analysis in this population showed all of these items to be part of the same unidimensional construct (**table 2-7, page 53**).

Medication concerns was measured by a 12-item scale that assessed patient perceptions regarding the perceived long-term safety of and dependence upon medications, and whether or not medications in their view are over-prescribed. This scale was developed from three subscales of the Beliefs about Medications Questionnaire(266) that assess concerns regarding medications that have specifically been prescribed for the patient, concerns that medications in general are harmful, and concerns that medications in general are overprescribed. However, principle components analysis within our sample showed these to all be measuring the same construct, with high internal consistency reliability (**table 2-7**).

Perceived susceptibility to fracture was assessed with 3 items from the four item scale of Gerand and colleagues(256) and *perceived severity of fractures* was also assessed with 3 *ad hoc* items developed for this study. We postulated that perceived susceptibility to fractures would not be associated with perceived need for fracture prevention medication if fractures were considered to have only trivial health consequences, and that conversely fractures perceived to have severe health consequences would not be associated with medication need if that person felt they were at minimal risk of experiencing the fracture. Therefore, we scaled the lowest score for both susceptibility to fracture and severity of fracture to equal zero, and

created a variable called *fracture susceptibility*severity* as the interaction between the two.

The *quality of the patient-provider relationship* was assessed with two previously validated scales; the 11 item Trust in Physician scale (assessing trust in the physician's competence and willingness to address the patient's concerns),(87, 88) the 5 item Open Communication Scale of the Medical Outcomes Study,(80) plus one *ad hoc* item assessing satisfaction with the decision making style of the provider. Factor analysis revealed that all 17 items strongly load on the same factor and together exhibited strong internal consistency reliability (**table 2-7**), and thus all were used together to assess the quality of the physician-provider relationship from the patient's perspective.

Fracture knowledge regarding the health consequences of fractures was assessed with a 6 item scale that we developed for this study to assess knowledge regarding possible health consequences of fractures. *Depression* was assessed with the three depression screening items of the SF-36D(254) assessing self-reported depressed mood in the recent or more distant past. This was scored dichotomously as present if any of the three were endorsed, and as absent if all three items were not endorsed. To the extent that depression correlates with pessimism regarding adverse future events, we postulated that depression outlook might be positively associated with perceived susceptibility to fracture and with concerns about the long-term safety of medications

Principal components analysis using orthogonal rotation for all of items from the above seven scales showed that all items were associated with their postulated factor with loadings >0.4, and were not associated any other factor with a loading >0.3. Internal consistency reliability (Cronbach's alpha) was lowest for the depression and knowledge scales but was over 0.8 for all of the other scales, and highest for the patient-provider relationship quality (**table 2-7**).

A personal history of spine, hip, wrist, pelvis, or upper arm fracture was assessed by self-report, as was a history of spine or hip fracture in a first degree relative (sibling or parent).

Control Variables – from medical record review

Medical record review was done for all 729 full respondents and also for all others (380) who were not deceased, had not actively refused participation, and who had been prescribed neither IV bisphosphonates nor teriparatide between January 1, 2006 and March 31, 2007. If one or more bone density tests had been done, bone mineral density of the lumbar spine, total hip, femoral neck, and/or the forearm from the test done nearest in time to January 1, 2006 was recorded.

Lateral spine imaging can be done on a bone densitometer to assess for prevalent vertebral fracture (vertebral fracture assessment), and are important predictors of subsequent fractures independent of bone mineral density. Two-thirds to three-quarters of vertebral fractures occur without acute symptoms, and their presence is unknown without spinal imaging. Vertebral fracture assessment (VFA) is done routinely for all patients at the time of bone densitometry at Park Nicollet if they are of age 65 or older and have a lumbar spine, femoral neck, or total hip T-score of -1.5 or lower, and hence selection bias on the part of the ordering physician in terms of who gets a VFA image done and who does not is highly unlikely to be present. We recorded if a lateral spine image at the time of bone densitometry was done to assess for prevalent vertebral fracture, and if so, whether the presence or absence of one or more prevalent vertebral fractures was indicated in the bone density report.

Statistical Analysis

Sixty five individuals whose surveys were missing data one-half or more of the items making up any of the scales were excluded. The remainder of the missing data was filled in with statistical imputation, creating a univariate imputation model for each missing item using all other items as predictor variables. A posterior distribution for each missing variable was created from these models, and a value for each missing datum was randomly selected from these distributions and imputed into the dataset.

Individual Regression Analyses within Multivariate Model

While the overall statistical plan was to fit a path model corresponding to **figure 4-1**, we first fit each of the three regression models implicit in figure 4-1 individually to be sure, for each equation, that the residuals were not correlated with the predicted values or with any single individual predictor. Adjustment in all cases was made for age, educational status, income level, and sex, although these were in turn eliminated

one by one from the models if the p-values of their associations were >0.2. Additional covariates were added one by one as control variables, and retained in the final models if the p-value of their association was ≤ 0.2 or their retention was needed to prevent heteroscedasticity of the error term or correlation between any predictor and the error term of the regression. These additional covariates included glucocorticoid use, smoking status, self-reported number of doses of prescribed medication each day, depression, and in the case of medication concerns, personal history of fractures.

Perceived need for fracture prevention medication was modeled as the raw need scale score squared, in order to achieve a normal distribution. Ordinary least squares was used to regress perceived need squared on concerns about medications, perceived susceptibility to and severity of fractures, the patient-provider relationship quality, presence of prevalent vertebral fracture, personal history of fracture, family history of fracture, bone mineral density. The final model also included age, educational status, and glucocorticoid use as covariates. Ordinary least squares was also used to regress medication concerns on the patient-provider relationship quality, and the final model included age, educational status, income, depression, and personal history of fracture as covariates.

Finally, perceived susceptibility to and severity of fractures was modeled as the raw score to the 0.7 power, in order to achieve a normal distribution. Ordinary least squares was used to regress the transformed susceptibility*severity score on the patient-provider relationship quality, bone mineral density, personal history of fracture, family history of fracture, and fracture knowledge. Age was included as an additional covariate in the final model.

The strength of the associations between the three continuous dependent variables and their predictors were expressed as the change of number of standard deviations of the dependent variable per unit or standard deviation change of the predictor, analogous to an effect size.

Multivariate Path Model and Instrumental Variables Analysis

The multivariate path model consisted of the three simultaneous OLS regressions described above, using MPLUS 5.1. All results were standardized to the standard deviations of the dependent variable, such that the expressions of the associations within the model were analogous to effect sizes.

To evaluate for the possibility of correlations between the error terms of the simultaneous regressions biasing the parameter estimates in the multivariate model, an instrumental variables regression analysis was performed in Stata 9.1. The first OLS regression model treated the variables concerns about medications and fracture susceptibility*severity as exogenous variables. The second model was an instrumental variables two-stage least squares (2SLS) regression performed with the *ivreg* command in Stata 9.1 that used bone mineral density, personal history of fracture, family history of fracture, age, educational status, income level, the number of medication doses per day, the patient-provider relationship quality, and depression as instruments for concerns about medication and fracture susceptibility*severity. Of these instruments, personal history of fracture, family history of fracture, depression, income level, and the number of daily doses of prescription medications per day were judged to be uncorrelated with perceived need for medication based on the first model. The significance of differences between the parameters estimates from the two models was evaluated with a Hausman model specification test.

Results

Surveys were mailed to all 1179 individuals within the Park Nicollet care system who appeared to met all inclusion and exclusion criteria, but medical record review subsequently showed that 20 had received either intravenous bisphosphonate medication or subcutaneous teriparatide during the period January 1, 2006 through March 31, 2007, were deceased, had never been prescribed an oral bisphosphonate, or had documentation of dementia. Hence the denominator to determine our response rate was 1,159 eligible participants, and among these 794 returned surveys, 4 surveys were returned as undeliverable, and 50 recipients called back actively refusing participation. Sixty-five respondents were excluded because more than one-half of the items for one or more of the scales measuring predictor variables were not answered. The final response rate was 729 of 1159, or 62.9%. Among these 729 respondents, 59% sent their survey back by July 31, and 97% had returned their survey by August 31, 2007. Complete data was present for 510 (70%) and for the remaining 219 survey respondents a mean 1.26 items (of a total of 57) per participant had to be imputed.

The characteristics of the 729 respondents with useable survey data and 380 non-respondents are shown **table 3-2 (page 79)**. Respondents were nearly two years

older, were slightly more likely to have an active, current prescription for an oral bisphosphonate recorded in the medical record at the time the survey was mailed, had more adverse drug reactions in the medical record than non-respondents, and slightly more likely to be current smokers. Non-respondents and respondents were no different with respect to sex, weight, bone mineral density, documentation of prevalent vertebral fracture, or use of oral glucocorticoids or proton pump inhibitors. Among respondents, 24.4% had less than a high school education, 23.9% were college graduates, nearly one-third had a personal history of fracture, and one-third had a family history of spine or hip fracture in a first degree relative.

The associations of predictor variables with perceived need for fracture prevention medication estimated from a single OLS regression are shown in **table 4-1** (column 2)**.** Each standard deviation increase in fracture susceptibility*severity was associated with a 0.31 (95% C.I. 0.24 to 0.38) standard deviation change of perceived need for fracture prevention medication. For each standard deviation increase in medication concerns, there was a small negative effect (-0.17 standard deviations, 95% C.I. -0.24 to -0.08) on perceived need for medication. The patient-provider relationship quality had a modest direct effect of (0.24 standard deviations, 95% C.I. 0.17 to 0.31) on perceived need for medication. A 10 year increase in age had a small negative effect (-0.13, 95% C.I. -0.21 to -0.06) on perceived need for fracture prevention medication. Those with a high school education or more may have had a slightly lower perceived need for fracture prevention medication compared to those with less than high school education, but these effects were of marginal significance. Chronic glucocorticoid use was not associated with perceived need.

Multivariate Path Model Results

The results of the multivariate path model are shown in **figure 4-2,** with all results expressed as standardized effects (change of number of standard deviations of the dependent variables). The total variance of perceived need for fracture prevention medication, fracture susceptibility*severity, and concerns about medications explained by the model were, respectively, 21.1%, 15.1% and 15.1%.

The parameter estimates and their standard errors for the direct effects of fracture susceptibility*severity, medication concerns, age, bone mineral density, and the patient-provider relationship quality on perceived medication need were nearly

identical to the estimates yielded by the single equation OLS model. In addition to its direct effect, however, patient-provider relationship quality had a moderate negative direct effect on concerns about medications (-0.31, 95% C.I. -0.38 to -0.24) and therefore an additional small indirect effect on perceived need for medication (0.05, 95% C.I. 0.02 to 0.08) through medication concerns. For each standard deviation increase of patient-provider relationship quality, there was a corresponding total effect of 0.29 (95% C.I. 0.20 to 0.37) on perceived need for medication. A 10 year increase in age had a small negative effect (-0.12, 95% C.I. -0.18 to -0.06) on perceived need for fracture prevention medication.

The direct effect of vertebral fracture assessment (VFA) appears much weaker in the multivariate model (0.13 standard deviations change in perceived need, 95% C.I. 0.02 to 0.24) than in the single equation OLS model. However, two-thirds did not have a VFA done, and MPLUS (the software with which the multivariate analysis was done) cannot estimate the specific effect on perceived need for medication of a VFA image positive for prevalent vertebral fracture compared to a VFA image negative for vertebral fracture excluding the contribution (or lack thereof) of unknown vertebral fracture status.

A one unit increase in bone mineral density t-score had a modest negative standardized effect of -0.20 (95% C.I. -0.33 to -0.07) on perceived fracture susceptibility*severity and had a weak but insignificant direct negative effect on perceived need for fracture prevention medication (-0.08, 95% C.I. -0.19 to 0.03). Family and personal history of fractures, respectively, had modest effects of 0.26 (95% C.I. 0.12 to 0.40) and 0.16 (95% C.I. 0.02 to 0.30) on perceived fracture severity*susceptibility, compared to those without family history and personal history of fracture. Similarly, a one quartile increase of fracture knowledge had a standardized effect of 0.25 (95% C.I.0.18 to 0.32) on fracture susceptibility*severity. Depression also had a moderate effect (0.32, 95% C.I. 0.17 to 0.46) on fracture susceptibility*severity. Personal history of fracture, family history of fracture, fracture knowledge, and depression had no direct effects on perceived need for fracture prevention medication. Unexpectedly, a prevalent vertebral fracture on a lateral spine DXA image was not associated with perceived fracture severity*susceptibility.

The indirect effects of other objective indicators of fracture risk and of fracture knowledge on perceived need for medication were statistically significant but small

(**table 4-2**). A one unit increase in bone mineral density T-score was associated with a small total effect on need for fracture prevention medication of -0.14 (95% C.I. -0.27 to -0.02) standard deviations. The effects of personal history of fracture, family history of fracture, and fracture knowledge were smaller.

Instrumental Variables Analysis

The parameter estimates for predictors of need for fracture prevention medication from the two-stage least squares regression with concerns about medications and fracture susceptibility*severity instrumented are shown in **table 4-1** (column 3) next to the standard single equation OLS estimates. Although the parameter standard errors are, as expected, wider with the instrumental variables analysis, the parameter point estimates of the standard OLS and instrumental variable regressions are similar, and no significant difference between them is evident from a Hausman test (chi-square 1.16, p-value 0.56).

Discussion

Perceived necessity of medication to preserve or improve one's health has been shown to be significantly predictive of persistence with medication used to prevent adverse events associated with a variety of chronic illnesses including chronic heart disease,(143) diabetes mellitus,(143) asthma,(145, 292) depression,(270) and chronic HIV infection.(146, 147) In the first paper of this project, we showed that perceived necessity of fracture prevention medication to be significantly associated with medication persistence.

In this analysis, we have shown that perceived susceptibility to and severity of fractures are associated with perceived need for fracture prevention medication, but only modestly so. Patient-provider relationship quality is also modestly associated with perceived need for fracture prevention medication, but some of this effect is indirect through its negative association with concerns about medication and the low but significant association of concerns about medication with perceived need for fracture prevention medication.

Perhaps most important, this study shows that documentation of a prevalent vertebral fracture on a lateral spine image obtained on a bone densitometer has substantial potential to influence perceived need for fracture prevention medication,

even after adjustment for multiple other factors including bone mineral density. Since a vertebral fracture assessment image was obtained for only one-third of our study participants, our study may underestimate the overall effect of vertebral fracture assessment on perceived need fracture prevention medication. This is important, because prevalent vertebral fractures are markers of those at highest risk of fractures(294, 295) who are most likely to benefit from fracture prevention medication. Lateral spine images for vertebral fracture assessment can be obtained quickly and inexpensively at the same time a bone density test is done, and increased utilization of vertebral fracture assessment at the time of bone densitometry may be a relatively easy way to improve utilization of pharmacologic fracture prevention therapy among those who will benefit from it most.

Unexpectedly, the effect of prevalent vertebral fracture was not indirect through perceived fracture susceptibility*severity, for unclear reasons. Possibly, individuals view kyphosis and its associated body image changes as a separate health consequence than fractures per se'. Alternatively, if prevalent vertebral fracture is associated with fracture prevention medication compliance, then use of medication may result in reduced perceived susceptibility to fractures.

Although a change of bone mineral density T-score of one unit confers a relative risk for subsequent non-vertebral fractures comparable to a prevalent vertebral fracture,(294, 296) this was only weakly associated with perceived need for fracture prevention medication. Moreover, personal history of fracture was only weakly associated with perceived fracture susceptibility and severity, and we could not demonstrate any association of either personal or family history of fracture with perceived need for fracture prevention medication. This raises the likelihood that patients are not fully or appropriately considering these factors when assessing their fracture risk and need for fracture prevention medication, and that better patient education on how fracture risk is related to specific aspects of their medical history may be needed. Consistent with this, the mean number of correct answers on the six item fracture knowledge scale was 2.95, indicating room for improvement for most patients with respect to their understanding of fracture risk and the health consequences of fractures.

The patient-provider relationship quality was not associated with perceived fracture susceptibility and severity, which could be interpreted that the uptake of

provider advice to patients about their fracture risk is not dependent on the quality of the patient-provider relationship quality. Alternatively, providers may not be leveraging the trust that their patient's have in them to influence how patients assess their fracture risk and need for fracture prevention medication. To address this, we would need to know the content of patient-provider interactions regarding the patient's fracture risk and medication to lower that risk. However, videotaped interactions of clinic encounters between patients and providers where new medications are being prescribed have shown that many aspects of the risks and benefits of the proposed new medication are not discussed.(275, 297) Further research will be needed to address the variability of patient-provider interactions where new fracture prevention medication is being considered, and how those interactions may be altered such that patients' perceptions of their fracture risk, the health consequences of fractures, and their perceived need for fracture prevention medication are more congruent with their actual risk.

Finally, this study suggests that concerns about the long-term harm of and dependence upon medications is negatively associated with perceived necessity for fracture prevention medication. This is in contrast to previously published formulations of the necessity-concerns framework, where both necessity and concerns are postulated to have independent effects on medication compliance but to have no association with each other.(143, 145, 237) However, it seems logical that if medications are viewed *in general* as potentially harmful, that an individual may be skeptical that maintenance of their health requires use of the medication even if they consider themselves to be at risk of the target condition and believe that the medication effectively reduces that risk.

There are many strengths of our study in general and this analysis in particular. This the first study to assess determinants specifically of perceived need for a medication to treat a chronic medical condition to prevent adverse future health events. Second, ours is the first survey study of medication attitudes and medication use behavior among those prescribed fracture prevention medication to include a medical record review such that important predictors of fracture such as bone mineral density and prevalent vertebral fracture could be assessed. Third, the good response rate to our survey was equivalent to or significantly better than other survey studies of medication use behavior.(41, 58)

Fourth, we employed a multivariate path model allowing for indirect effects of predictors on the dependent variable to be assessed. In contrast, when the associations of predictors with a dependent variable are assessed with a single equation regression model, then biased estimates of the association between a predictor and the dependent variable will result if the effect of one predictor on the dependent variable is in part indirect through another predictor. In this analysis, a single equation model would have underestimated the associations between perceived need for medication and both the patient-provider relationship quality and bone mineral density. While multivariate path models can also be biased from error term correlations between endogenous predictors and the dependent variable, we were able to rule out undue bias from such correlations with an instrumental variables analysis. Only one prior study has employed a multivariate path model with perceived necessity for medication as an endogenous predictor, but did not include objective measures of target condition risk in the model and did not assess for bias from error term correlations in their model.

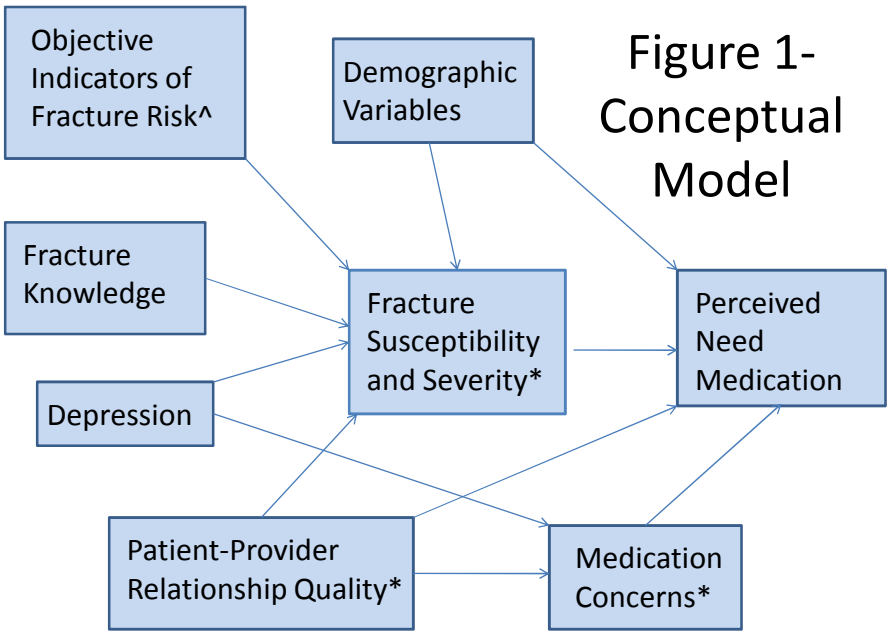
There are also important limitations to this study. First, those who did not respond to our survey were more likely to have more adverse drug reactions and to not have an active current prescription for a fracture prevention medication in the medical record, suggesting that responders may not be representative of the entire population for whom fracture prevention medication is prescribed. Non-responders may have had more perceived side effects to fracture prevention medications, or conceivably more concerns about the long-term risk of and/or dependence upon medications. It is also possible that osteoporosis and related fractures are less salient issues for non-respondents corresponding with a decreased sense of threat to their personal health from fractures, reduced need for fracture prevention medication, less interest in the topic, and therefore a lower proclivity to respond to the survey.

Second, our study population did not include those who were offered but refused an initial prescription for a medication prescription, since we depended on the recording of an initial prescription for a fracture prevention medication in the medical record to identify our study sample. Third, our study population was drawn from only one multi-specialty urban clinic in the United States and was overwhelmingly white and female, limiting the generalizability of our results. Finally, our model still only explains only 21% of the variance of perceived need for fracture prevention medication. We

were unable to assess numerous other potential predictors of perceived need for fracture prevention medication, including the effects of direct industry to consumer advertising by the pharmaceutical industry and the attitudes toward osteoporotic fractures, medications in general, and fracture prevention medication in particular within patients' social networks. Additionally, we did not assess time preference, the degree to which individuals plan for the future as compared to committing more of their financial, psychological, and time resources to current everyday concerns. Essentially, taking fracture prevention medication is the use of resources in the present time to reduce the risk of events that may or may not happen in the future. Those that are more concerned about present day issues in their day to day life either because of their magnitude or because of a general proclivity to discount future outcomes may perceive less of a need to prevent adverse future outcomes.

In conclusion, perceived need for fracture prevention medication is associated, as expected, with perceived susceptibility to and severity of fractures and the patient-provider relationship quality. Prevalent vertebral fracture on lateral spine DXA imaging is also associated with perceived need for fracture prevention medication, and vertebral fracture assessment at the time of bone densitometry may not only identify those at higher risk of incident fractures but also encourage appropriate perception of need to reduce that risk and subsequent compliance with fracture prevention medication. More studies are needed to identify how providers can improve the congruence of patients' perceived need for fracture prevention medication with their actual risk, and to investigate other potential predictors of perceived need for medication such as patients' social networks and their time preference.

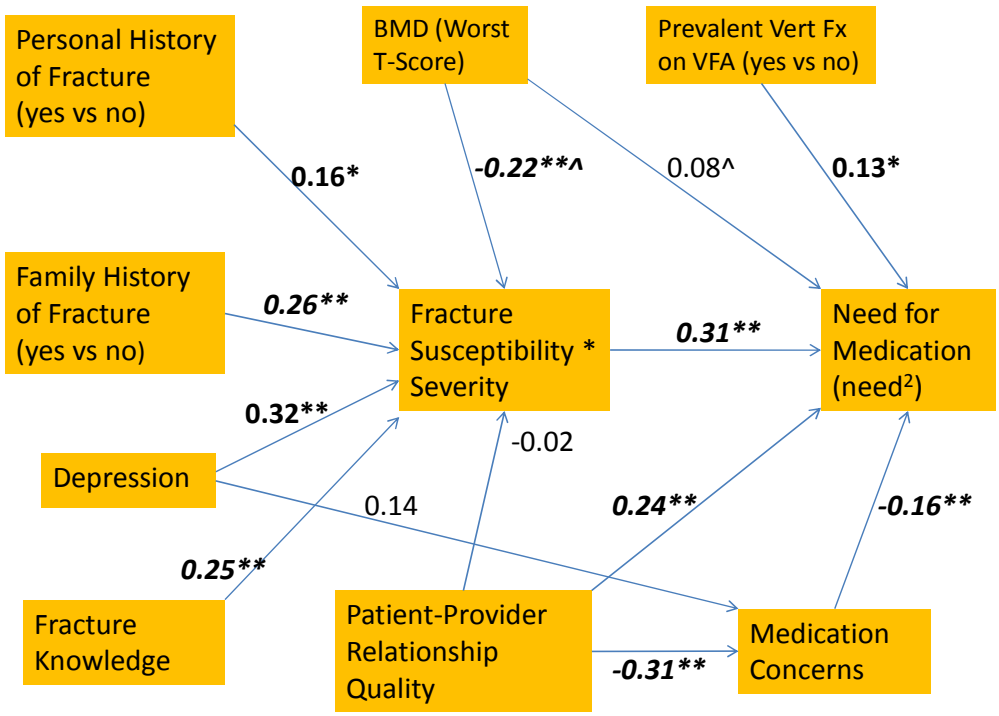
Figure 4-1: Conceptual Framework of Analyses with Perceived Need for Medication as the Dependent Variable



*****Endogenous predictors: predictors of perceived need for fracture prevention medication that are also dependent variables within the model

^Includes family history of fracture, prior history of fracture, prevalent vertebral fracture on lateral spine imaging, bone mineral density, chronic oral glucocorticoid use, and cigarette smoking

Figure 4-2: Final Multivariate Path Model of Predictors of Perceived Need for Fracture Prevention Medication



*P-value of association <0.05
**P-value of association <0.01

^Per one unit increase of worst T-score of lumbar spine, total hip, femoral neck, or distal forearm

Model Fit Statistics:
Chi-square 13.07, p-value 0.60
Comparative Fit Index 1.000
Root Mean Square Error of Approximation <0.001
Standardized Root Mean Square Residual 0.011

Table 4-1: Parameter Estimates for Standard Single Equation OLS and Instrumental Variables 2SLS Regressions of Need for Fracture Prevention Medication*^

Predictor	Standard OLS Estimate (95% C.I.)	Instrumental Variables 2SLS Estimate (95% C.I.)
Perceived Fracture Susceptibility*Severity$^{0.7}$ (Per SD)	**0.31 (0.24 to 0.38)**	**0.40 (0.21 to 0.60)**
Concerns about Medications (per SD)	**-0.17 (-0.24 to -0.10)**	-0.16 (-0.53 to 0.21)
Patient-Provider Relationship Quality (per SD)	**0.24 (0.17 to 0.31)**	**0.25 (0.11 to 0.39)**
Prevalent Vertebral Fracture	No: 0.0 (reference) Unknown: 0.08 (-0.08 to 0.25) Yes: **0.30 (0.24 to 0.57)**	No: 0.0 (reference) Unknown: 0.07 (-0.10 to 0.24) Yes: **0.31 (0.03 to 0.59)**
Bone Mineral Density T-score (per 1 unit increase)	-0.09 (-0.20 to 0.02)	-0.06 (-0.19 to 0.05)
Age (per 10 year increase)	**-0.13 (-0.21 to -0.06)**	**-0.12 (-0.20 to -0.04)**
Educational Status **Quartile 2 vs. 1:** **Quartile 3 vs. 1:** **Quartile 4 vs. 1:**	 -0.17 (-0.36 to 0.01) **-0.25 (-0.46 to -0.04)** -0.20 (-0.41 to 0.01)	 -0.19 (-0.37 to 0.00) -0.24 (-0.48 to 0.00) -0.22 (-0.47 to 0.03)
Glucocorticoid Use (Yes vs. No)	-0.16 (-0.42 to 0.10)	-0.18 (-0.44 to 0.09)

*****Need for fracture prevention medication modeled as raw score squared.

^Parameter estimates are expressed as number of standard deviations of medication need[2] , those significant at p<0.05 level are in **bold**

Hausman test for difference between OLS and Instrumental Variables 2SLS estimates: Chi-square 1.16, p-value 0.56

Table 4-2: Direct, Indirect, and Total effects of Objective Indicators of Fracture Risk and of Fracture Knowledge on Perceived Need for Fracture Prevention Medication*

Predictor	Direct Effect (95% C.I.)	Indirect Effect (95% C.I.)	Total Effect (95% C.I.)
Prevalent Vertebral Fracture (yes vs. no)**	0.30 (0.24 to 0.57)	0	0.30 (0.24 to 0.57)
Bone Mineral Density (per 1 T-score Increase)	-0.08 (-0.19 to 0.03)	-0.06 (-0.10 to -0.02)	-0.14 (-0.27 to -0.02)
Family History of Fracture (yes vs. no)	0	-0.08 (-0.13 to -0.03)	-0.08 (-0.13 to -0.03)
Personal History of Fracture (yes vs. no)	0	-0.05 (-0.09 to -0.00)	-0.05 (-0.09 to -0.00)
Fracture Knowledge (per 1 quartile increase)	0	0.07 (0.04 – 0.10)	0.07 (0.04 – 0.10)

*Effects expressed as changes in number of standard deviations of need[2]

**The direct effect of prevalent vertebral fracture on perceived need for fracture prevention medication in this table is derived from the single OLS regression equation in STATA, allowing the effect of a VFA positive for prevalent vertebral fracture compared to a VFA negative for prevalent vertebral fracture to be estimated

Chapter 5:

Influence of the Quality of the Physician-Patient Relationship on Medication Attitudes, Persistence, and Compliance

Abstract

Background: Persistence and compliance with fracture prevention medication among those with osteoporosis is suboptimal, such that only 50% or so of those prescribed a fracture prevention medication are still taking that medication one year later. Non-persistence and non-compliance with medication used to treat osteoporosis is associated with increased fractures and related health care costs. While some studies have shown that the quality of the relationship between the patient and the prescribing provider is a determinant of medication use behavior, the magnitude of the effect has never been estimated, and the additional effects of the patient-provider relationship quality this has never been investigated.

Objective: The primary objective was to estimate the association between self-reported non-persistence with oral fracture prevention medication and the patient-provider relationship quality. The secondary objective was to estimate whether the effect of the patient-provider relationship quality on non-persistence is direct or mediated through one or more four postulated mediators; perceived need for fracture prevention medication, concerns about the long-term safety of and dependence upon medication, medication use self-efficacy, and perceived medication cost burden.

Methods: We surveyed 1155 patients who had been prescribed an oral bisphosphonate medication to prevent fractures at a large metropolitan multi-specialty medical center between the dates of January 1, 2006 and March 31, 2007, to assess their self-reported medication use, medication attitudes, and other factors such as perceived susceptibility to and severity of fractures, and personal and family history of fracture. Medical record review was performed to results of bone mineral density testing, documentation of vertebral fractures, and history of adverse medication reactions. A multivariate path model was employed to estimate the effects of the patient-provider relationship quality on non-persistence, both direct and indirect through the postulated mediating variables. Instrumental variables analyses were done to test for regression error term correlations within the multivariate model. Single-equation probit regression models were used to assess the direct effect of the patient-provider relationship quality on non-persistence and the attenuation of this effect by adding in the postulated mediators to the model.

Results: The patient-provider relationship quality was modestly but significantly associated with self-reported non-persistence, such that with all other predictors and covariates at their mean value, a one standard deviation increase in the patient-provider relationship quality would reduce the probability of non-persistence from 34.2% to 28.5%. Half of this effect appears to be mediated by perceived need for fracture prevention medication, with lesser proportions mediated by medication concerns, and medication use self-efficacy.

Conclusion: Providers who have a better relationship with their patients at high risk of fracture may be better able to influence those patients' perceived need for fracture prevention medication, alleviate concerns about the long-term safety of and dependence upon those medications, and influence medication use self-efficacy, and thereby positively influence persistence with fracture prevention medication.

Introduction

Osteoporosis is a condition that results in loss of bone strength through both loss of bone mineral density and micro architectural deterioration of the bone, and its prevalence rises sharply with age in both men and women. Woman and men age 60, respectively, have a 44% and 25% chance of having a fracture related to osteoporosis during their remaining lifetime.(259) The oral bisphosphonates are the most common type of medication used to preserve or improve bone strength and reduce fractures by 30 to 50%.(260, 264, 286) However, numerous descriptive studies have shown that within 1 to 2 years of being prescribed an oral bisphosphonate medication, only 32 to 68% are still taking it.(28, 29) This pattern of non-persistence has also been demonstrated in studies of oral medication used to prevent adverse health events associated with other chronic conditions such as hypertension,(24, 25, 288, 289) hyperlipidemia,(26, 27) and asthma.(290)

Few studies, however, have been done to date that have tried to explain why the phenomenon occurs. A large literature has also arisen over the past two decades that suggests the quality of the patient-provider relationship is significantly associated with uptake of and compliance with health behaviors recommended by the provider.(80, 288, 298-300) Three qualities in particular are postulated to be of importance, called open communication style, decision making congruence, and trust in the physician. *Open communication style* refers specifically to how well the provider shares information regarding the options available to manage the health concern, and their advantages and disadvantages.(301) *Congruence in decision making* refers to the degree to which, from the patient's perspective, the decision making style of the provider is congruent with the extent to which the patient wishes to take an active role in decision making regarding their health management.(81) *Trust in physician* has been conceptualized by Hall and colleagues as composed of four attributes; the level to which the patient has faith that the physician will pursue their best interests and not take advantage of their vulnerability, believes that the physician is knowledgeable and competent, and that the physician will be honest with them, and will protect their confidentiality.(89) Several studies have shown that open communication,(300, 302, 303) satisfaction with the provider's decision making style,(304, 305) and trust in their physician(88, 180, 305) are correlated with medication compliance and persistence among those with diabetes, acquired immune deficiency syndrome, depression, and

medication prescriptions as an undifferentiated group in primary care practices, but no studies have investigated the association of patient-provider relationship qualities and compliance with fracture prevention medication to prevent fractures associated with osteoporosis. Moreover, no study to date has estimated what proportion of the phenomena of non-compliance and non-persistence is explained by these patient-provider variables, and therefore what effect might be seen on compliance and persistence by maximizing those variables. Finally, none of the studies done to date have elucidated the mechanisms by which these patient-provider relationship characteristics may influence medication use behavior.

Horne and colleagues have conceptualized patient willingness to comply with medication prescriptions as being the difference between perceived necessity of medications and concerns about negative effects of medications (including long-term safety of and dependence upon medications), and have shown that these variables are predictive of compliance among patients with diabetes, asthma, heart failure, renal failure, and acquired immune deficiency syndrome (AIDS).(142, 143, 147) The associations of these specific postulated predictors of medication compliance, however, have not been investigated among patients with osteoporosis. It is conceivable that patient-provider relationship characteristics affect compliance directly, or indirectly by influencing patient perceptions of the necessity of prescribed medications to preserve their health and of the safety of these medications. Studies of patient preferences regarding fracture prevention medication among those with osteoporosis have suggested that they will be reluctant to use medication recommended to them by a physician if they are not convinced of its effectiveness and long-term safety.(58, 272, 277, 279, 306) A recent study among those prescribed oral bisphosphonate medication for osteoporosis showed their perceptions regarding the effectiveness of the medication and concerns about its long-term safety were predictors of compliance to the drug, independent of side effects.(41)

The primary aim of this study was to assess the association of the provider-patient relationship quality with persistence with oral bisphosphonate medication (the most common family of medications used to treat osteoporosis), both directly and indirectly through other variables such as perceived need for medication and concerns about medications. Secondary aims were to estimate the association of the patient-

provider relationship quality on attitudes regarding both the target condition being treated (osteoporosis) and the medications used to treat it.

Methods

This study was reviewed and approved by the Institutional Review Boards of both Park Nicollet Heath Services and the University of Minnesota.

This dataset is from a survey and medical record review of patients given one or more prescriptions for oral bisphosphonate therapy at Park Nicollet Clinic between the dates of January 1, 2006 and March 31, 2007. Candidate participants were those age 21 to 84 with one or more prescriptions for an oral bisphosphonate medication in the electronic medication record in this time period, who had had a clinic visit within 6 months of the mailing date of the survey (to assure they were still receiving care at Park Nicollet Clinic) and did not have a diagnosis of dementia.

Potential study participants were mailed the survey during the week of July 16 through July 20, 2007. Those who had not returned the survey within two weeks were mailed a reminder postcard. Those who had still not returned the survey or called in to actively refuse participation were mailed a second survey one month later. Among the subset of survey respondents, 59% sent their survey back by July 31, and 97% had returned their survey by August 31, 2007.

Conceptual Framework

We conceived the possible effects of the perceived patient-provider relationship quality on medication persistence with fracture prevention medication in the context of the health belief model.(92) We postulated a possible direct effect of the patient-provider relationship quality on medication persistence, but that the bulk of the effect on persistence would be primarily indirect through perceived need for medication, concerns long-term safety of and dependence upon medication, medication use self-efficacy, and possibly perceived medication cost burden (**figure 2-1, page 30**). We also postulated that the perceived patient-provider relationship quality might influence fracture knowledge and perceived susceptibility to and severity of fractures, but that the effects of these two variables on medication persistence would be indirect through perceived need for medication.

Where possible, scales to measure these constructs were derived from previously validated scales, but for some constructs we were unable to find any appropriate measures and hence developed new scales to measure these. The unidimensionality of these scales was assessed using principle components analysis of all scale items together, and also from principle components analyses of each scale separately. A ratio of the first to second eigenvalue of greater than 2.0 was considered to be strong evidence of unidimensionality for each scale.

Dependent Variables

Self-reported persistence was assessed with two questions; whether or not the patient had stopped taking their oral bisphosphonate for more than one month due to side effects, whether or not the patient had stopped taking their oral bisphosphonate for more than one month for reasons other than side effects. A variable of self-reported non-persistence for any reason was created if they answered "yes" to either question.

Predictor Variables – from survey items

The *quality of the patient-provider relationship* in this dataset was assessed with two previously validated scales; the 11 item Trust in Physician scale (assessing trust in the physician's competence and willingness to address the patient's concerns),(87, 88) the 5 item Open Communication Scale of the Medical Outcomes study,(80) plus one *ad hoc* item assessing satisfaction with the decision making style of the provider. Factor analysis revealed that all 17 items strongly load on the same factor and together exhibited strong internal consistency reliability (**table 2-7, page 46**), and thence all were used together to assess the quality of the physician-provider relationship from the patient's perspective.

Perceived necessity of fracture prevention medication was assessed by seven item scale, adapted from the validated four item medication necessity scale of Horne and colleagues,(142) with three additional items added to improve its internal consistency reliability. *Medication concerns* was measured by a 12-item scale that assessed patient perceptions regarding the perceived long-term safety of and dependence upon medications, and whether or not medications in their view are over-prescribed. This scale was developed from three subscales of the Beliefs about

Medications Questionnaire that assess concerns regarding medications that have specifically been prescribed for the patient, concerns that medications in general are harmful, and concerns that medications are in general are overprescribed.(142) However, principle components analysis within our sample showed these to all be measuring the same construct, with high internal consistency reliability (**table 2-7**).

Perceived susceptibility to fracture was assessed with 3 items of Gerand and colleagues(256) and *perceived severity of fractures* was also assessed with 3 items developed for this study. We postulated that perceived susceptibility to fractures would not be associated with perceived need for fracture prevention medication if fractures were considered to have only trivial health consequences, and that conversely fractures perceived to have severe health consequences would not be associated with medication need if that person felt they were at minimal risk of experiencing the fracture. Therefore, we scaled the lowest score for both susceptibility to fracture and severity of fracture to equal zero, and created a variable called fracture susceptibility*severity as the interaction between the two.

Fracture knowledge regarding the health consequences of fractures was assessed with a 6 item scale that we developed for this study, that assess knowledge regarding possible health consequences of fractures. *Medication use self-efficacy* was measured with 7 item selected from the validated scale of Resnick and colleagues,(209) assessing how confident patients felt they could execute medication use behavior in the context of their daily lives. *Depression* was assessed with a three items assessing self-reported depressed mood in the recent or more distant past as well as current and/or past use of anti-depressant therapy. This was scored dichotomously as present if any of the three were endorsed, and as absent if all three items were not endorsed. *Medication cost burden* was assessed with one item.

Principle components analysis using orthogonal rotation for all of items from the above seven scales showed that all items were associated with their putative factor with loadings >0.4, and did were not associated any other factor with a loading >0.3. Internal consistency reliability (Cronbach's alpha) was lowest for the depression and knowledge scales but was over 0.8 for all of the other scales, and highest for the patient-provider relationship quality (**table 2-7**).

A personal history of spine, hip, wrist, pelvis, or upper arm fracture was assessed by self-report, as was a history of spine or hip fracture in a first degree relative.

Control Variables – from medical record review

We postulated that that those with prior bad experiences with medications may be more likely to attribute adverse medical events or symptoms to their fracture prevention therapy and stop taking it for this reason, and assessed this as the number of adverse medication reactions (ADR's) recorded in the medical record (excluding bisphosphonates). Since the most common side effect leading to discontinuation of oral bisphosphonates is stomach upset, we postulated that a gastric acidity disorder such a gastro-esophageal reflux disease would predispose individuals to stop oral bisphosphonate therapy on account of perceived side effects. We assessed whether or not a prescription for more than one month of a proton pump inhibitor had been recorded in the medical record as a surrogate marker of gastric acidity disorder. Smoking status is recorded at each clinic encounter at Park Nicollet Clinic as a "vital sign", and current cigarette smoking was postulated to be positively associated with perceived susceptibility to fractures, but to the extent that smoking is associated with less concern for one's health, to be negatively associated with perceived need for fracture prevention medication mediation persistence and compliance. If one or more bone density tests had been done, bone mineral density of the lumbar spine, total hip, femoral neck, and/or the forearm from the test done nearest in time to January 1, 2006 was recorded.

Since prior fracture and low BMD are both predict incident fracture independent of each other, a three level ordinal variable called "Fracture Risk" was created, with the first level being the absence of both osteoporosis by BMD criteria or a personal history of fracture, the second level being the presence of either a history of fracture or osteoporosis by BMD criteria, and the third level being the presence of both osteoporosis by BMD criteria *and* a prior history of fracture.

Statistical Analysis

Individuals whose surveys were missing data one-half or more of the items making up any of the scales were excluded. The remainder of the missing data was filled in with statistical imputation, creating a univariate imputation model for each

missing item using all other items as predictor variables. A posterior distribution for each missing variable was created from these models, and a value for each missing datum was randomly selected from these distributions and imputed into the dataset.

Validation of Self-Report Measures of Medication Use Behavior

Validation of self-reported persistence and self-reported missing of doses was done in two ways. Pharmacy claims data for oral bisphosphonate use between the dates of January 1, 2006 and March 31, 2007 were available for that subset of study participants whose health insurer was HealthPartners (n=82), as Park Nicollet clinic had access to pharmacy claims for those patients designating Park Nicollet clinic as their health care provider. The Medication Possession Ratio (MPR) was calculated as the ratio of the number of days of medication available for use as prescribed between the first and last prescriptions divided by the total number of days between the first and last prescriptions. A dichotomous variable was created, with “non-compliance” defined as an MPR < 0.8, and “compliance” defined as an MPR ≥ 0.8. Agreement between overall non-persistence and compliance as defined by MPR was assessed using kappa statistics (**table 3-1, page 78**). Non-persistence was also assessed by medical record review, and medical record non-persistence defined as documentation in the medication section of the medical record of an oral bisphosphonate being stopped and the passage of more than one month before the same or another fracture prevention medication being prescribed. Agreement between overall non-persistence and medical record non-persistence was assessed using kappa statistics (**table 3-1**).

Individual Regression Analyses within Multivariate Model

While the overall statistical plan was to fit a path model corresponding to **figure 2-1**, we first fit each of the six regression models implicit in figure 2-1 individually to be sure, for each equation, that the residuals were not correlated with the predicted values or with any single individual predictor. For those cases where the dependent variable was ordinal with more than two categories, we made certain that the proportional odds assumption was met. Transformations for two variables were done such that their distributions were normal; need for fracture prevention medication was modeled as the raw perceived need score squared, and fracture susceptibility*severity was modeled as its raw score to the 0.7 power.

A probit regression model was used to estimate the association between self-reported non-persistence and the patient-provider relationship quality, perceived need

for fracture prevention medication, concerns about harm from and dependence upon medications, perceived self-efficacy for taking medications, and perceived medication cost burden, adjusted for the use of proton pump inhibitor, the number of ADRs recorded in the medical record, age, sex, educational status, income, use of oral glucocorticoid medication, smoking status, and disease duration. Ordinary least squares (OLS) An estimated the associations between perceived need for fracture prevention medication and the patient-provider relationship quality and the perceived fracture susceptibility*severity, adjusted for age, sex, educational status, income level, personal history of clinical fracture, family history of fracture, prevalent vertebral fracture, and bone mineral density.

Ordinary least squares (OLS) regression was also used to assess the association between concerns about medications and the patient-provider relationship quality, adjusted for depression, personal history of fracture, family history of fracture, the number of ADR's in the medical record, age, sex, educational status, and income level. A probit model was used to regress medication use self-efficacy on the patient-provider relationship quality, depression, number of prescribed daily doses of medication, age, sex, income and educational status. OLS regression was also used to estimate the associations between perceived fracture suspectibility*severity and fracture knowledge and the patient-provider relationship quality, adjusted for BMD, personal history of fracture, family history of fracture, age, sex, educational status, and income level. Finally, an ordinal probit model was used to estimate the association of medication cost burden with the patient relationship, adjusted for age and income.

For each regression model, backward elimination was done to remove variables other than the patient-provider relationship quality one by one with p-values for associations with the dependent variable >0.2, unless removal of said predictor resulted in heteroscedasticity, association of the any predictor being associated with the error term of the regression, or violation of the proportional odds assumption (ordinal probit models).

Path Model

The associations between the five dependent variables and their predictors retained in the final regression models were estimated with a multivariate model, using MPLUS version 5.1. The full model allowed direct paths between the four variables

postulated to mediate the association between the patient-provider relationship quality and non-persistence (**figure 5-1**), whereas the restricted model allowed only a direct path from the patient-provider relationship quality and non-persistence (**figure 5-2**).

The coefficients for paths where the predictor and/or dependent variables were modeled as continuous variables were standardized to the standard deviation(s) of those continuous variables. Standardized path coefficients were multiplied to assess the indirect effect of the patient-provider relationship quality on medication non-persistence through a mediating variable. The total indirect effect of the patient provider relationship quality on medication non-persistence was then calculated as the sum of all of the individual indirect path effects. The goodness of fit of the multivariate models was determined by chi-square statistic, the comparative fit index (excellent fit generally being a CFI score higher than 0.9)(307), and the root mean square error of approximation (excellent fit generally being an RMSEA of < 0.05).(308)

The primary analytic models, however, leave open the possibility of biased parameter estimates due to correlations between the error terms of the constituent regressions within the multivariate model, which in turn can be due to omitted variables or reverse causality. Three additional analyses were done to address this problem. First, the restricted path model was used to estimate the total effect of the patient-provider relationship quality on non-persistence. To further illustrate the significance of the effect of the patient-provider relationship quality on medication non-persistence, the predicted probability of non-self-reported non-persistence was then calculated for one and two standard deviation changes from the mean of the patient-provider relationship quality score, keeping all other variables at their mean levels.

Second, an instrumental variables regression utilizing the *ivprobit* command of Stata 9.1 was run using demographic variables, objective indicators of fracture risk, fracture knowledge, depression, and the patient-provider relationship quality as instruments for perceived need for medication and concerns about medications. Since we are also postulating a direct effect of concerns about medications on perceived need for medication, two sets of analyses were done, the first set using instruments only for perceived need with concerns about medications included as one of the instruments, and a second set using instruments for both perceived need for medication and concerns about medications. These models were first estimated in one step with a maximum likelihood estimator, but if convergence could not be achieved,

then a two-step estimator(269) was used. Wald tests were done to assess if the error terms of these two regressions were correlated.

Third, the mediation of the effect of the patient-provider relationship quality and non-persistence by the proposed mediating variables was also tested with a single equation probit regression model. The multivariable adjusted association of the association between the patient-provider relationship quality and non-persistence was first estimated without inclusion of the proposed mediators. The mediators were then added one by one to the model, and the attenuation of the association between patient-provider relationship quality and non-persistence noted.

Results

Surveys were mailed to all 1179 individuals within the Park Nicollet care system who met all inclusion and exclusion criteria, and 807 were returned. Four surveys were returned as undeliverable and 50 recipients called back actively refusing participation. Seven of the remaining non-respondents and 13 respondents were excluded because medical record review showed that they had received either intravenous bisphosphonate medication or subcutaneous teriparatide during the period January 1, 2006 through March 31, 2007, were deceased, had never been prescribed an oral bisphosphonate, or had documentation of dementia on further review of their medical record. Sixty-five were excluded because more than one-half of the items for one or more of the scales measuring predictor variables were not answered. The final response rate was 729 of 1155, or 63.1%. Complete data was present for 510 (70%) and for the remaining 219 participants a mean 1.26 items (of a total of 57) per participant had to be imputed.

The characteristics of the 729 respondents with useable survey data and 380 non-respondents are shown **table 3-2, page 79**. Respondents were nearly two years older, were slightly more likely to have an active, current prescription for an oral bisphosphonate recorded in the medical record at the time the survey was mailed, had more adverse drug reactions in the medical record than non-respondents, and has slightly more current smokers. Non-respondents and respondents were no different with respect to sex, weight, bone mineral density, documentation of prevalent vertebral fracture, or use of oral glucocorticoids or proton pump inhibitors. Among respondents, 24.4% had less than a high school education, 23.9% were college graduates, nearly

one-third had a personal history of fracture, and one-third had a family history of spine or hip fracture in a first degree relative.

Path Model Relationships

The overall fit of the restricted model (**figure 5-2)** was very good (chi-square 49.85, degrees of freedom 43, p-value 0.14; CFI 0.962; RMSEA = 0.019), and showed a modest direct effect of the patient-provider relationship quality on medication non-persistence (parameter estimate -0.16, p-value = 0.005). With all other predictors set to their mean values, a one standard deviation increase of the patient-provider relationship quality from its base mean value reduces the probability of self-reported non-persistence 5.7% (from 34.2% to 28.5%). Those with a patient-provider relationship quality score 2 standard deviations below the mean had an estimated probability of self-reported non-persistence with fracture prevention medication of 46.5%, whereas those with a patient-provider relationship quality score 2 standard deviations above the mean had an estimated probability of self-reported non-persistence with fracture prevention medication of 23.3%.

The full model also showed excellent fit (chi-square 45.8, p-value 0.24, CFI 0.978, and RMSEA = 0.015), and substantial effect of perceived need for fracture prevention medication on non-persistence, with lesser effects of medication concerns and medication use self-efficacy on non-persistence, and no significant direct effect of the patient-provider relationship quality (p-value 0.81) or of medication cost burden (p-value 0.31) on non-persistence (**figure 5-1**). The apparent total effect of the patient-provider relationship quality on non-persistence was slightly higher (-0.175) than estimated with the restricted model, consistent with introduction of some bias by the inclusion of endogenous predictors in the model. Forty two percent of the total effect of the patient-provider relationship quality appeared to be solely through perceived need for fracture prevention medication (standardized indirect effect -0.081), 20.6% solely through concerns about medication (indirect effect -0.039), 9.5% through both medication concerns and perceived medication need (indirect effect -0.018) and 21.1% through medication use self-efficacy (indirect effect -0.040).

Instrumental variables analyses, first using instruments only for perceived need for medication and then second for both perceived medication need and for concerns about medications, showed no evidence of correlations between error terms of the

regressions for perceived need for medication, concerns about medications, and non-persistence (**table 5-1**). However, since we could not create instruments for medication use self-efficacy and perceived medication cost burden, we could not test for correlations between the error terms of the regressions for medication use self-efficacy, perceived medication cost burden, and non-persistence

When a single-equation probit regression model is employed, the multivariable-adjusted standardized parameter estimate for the effect of the patient-provider relationship quality on non-persistence is again -0.16 (**table 5-2**). The parameter estimate was only -0.08 after addition of perceived need for fracture prevention medication as a predictor, and only -0.016 after addition of all of the mediators. Very similar results were obtained when the mediating variables were added in the reverse order (data not shown).

Discussion

Persistence with medication to prevent osteoporotic fractures has now been shown in several observational studies to be low. Moreover, medication persistence has been shown to be associated with greater reduction of fractures related to osteoporosis(59, 61, 63) and health care costs.(60)

In this cross-sectional survey and medical record review study, we have shown that the quality of the patient-provider relationship from the patient's perspective is modestly associated with self-reported fracture prevention medication non-persistence. The full multivariate path model suggests that about half of the effect of the patient-provider relationship quality on self-reported non-persistence is through perceived medication need, and a quarter through concerns about medication. Although the multivariate model cannot estimate precisely the indirect effects of the patient-provider relationship quality is through medication use self-efficacy and perceived medication cost burden, the single probit regression models suggest that the remainder of the effect of the patient-provider relationship quality on non-persistence is through these two mediating variables. There appears to be little if any direct effect of the patient-provider relationship quality on self-reported non-persistence with fracture prevention medication.

Numerous qualitative research studies have shown that patients are much more likely to view a provider's recommendation to commence a medication to treat a

chronic illness skeptically if they do not have trust in the physician's competence and willingness to share all relevant information with them,(79, 80, 87, 300, 309-311) and/or are uncomfortable with their physician's decision making style.(80, 81, 299) Our study is the first to investigate the association of the patient-provider relationship quality with non-persistence to medication used to treat osteoporosis, and with medication attitudes that in turn are powerful predictors of medication non-persistence. Our results show several ways that a good patient-provider relationship could be leveraged to influence patient use of fracture prevention medication. Specifically, clearly illustrating the patient's personal risk of fractures and the potential severe health consequences of fractures are likely to influence their perceived need for medication. Eliciting and addressing concerns patient's may have about the long-term safety of fracture prevention medication and discussing strategies to more easily execute medication use in the context of one's daily life may also positively influence fracture prevention.

At first glance it may seem surprising that this study did not show a stronger association of the patient-provider relationship quality with fracture prevention medication persistence. However, we did not assess the *content* of conversations providers had with study participants when recommending pharmacologic fracture prevention therapy. Recent studies have shown that when new medications are prescribed, side effect risks are thoroughly discussed in a minority of these health care encounters.(297) No study, to our knowledge, has specifically analyzed the content of conversations providers have with their patients who are at high risk of fractures regarding fracture prevention medication. However, Pickney and colleagues have recently shown in a cohort of post-menopausal women that only half of those with osteoporosis by bone density criteria could accurately recall their bone density test results and were aware that they had osteoporosis.(56) Among our study participants who had patient-provider relationship quality scores above the mean, only 36% of those who had osteoporosis by BMD criteria *and* a self-reported prior fracture knew the correct answers to more than half of the knowledge questions regarding the health consequences of fractures, only 44% thought they were at high risk of fractures, 34% thought that hip and spine fractures would not pose substantial risk to their health should they occur, and nearly a quarter had a perceived need for fracture prevention medication in the lowest quartile. This suggests that providers may not be fully communicating to patients at the highest risk of fracture the health consequences of

those fractures and the potential benefit from pharmacologic fracture prevention therapy, leveraging the trust that their patients have in them.

New guidelines from the World Health Organization,(312, 313) the International Osteoporosis Foundation in Europe,(314) and the National Osteoporosis Foundation in the United States(315) recommend offering pharmacologic fracture prevention therapy to those with an estimated absolute 10 year fracture risk above a specific threshold, rather than for those with a bone density level below a specific threshold. This may help focus the attention of patients with osteoporosis specifically on their susceptibility to fracture. However, we believe that to further improve persistence with pharmacologic fracture prevention therapy, providers will also have to specifically elicit and address under-appreciation of the adverse health consequences of fractures, concerns that patients have regarding the long-term safety and dependence upon fracture prevention medication, and any concerns patients may have regarding their ability to afford medications or execute their use in the context of their daily lives. We further postulate that these efforts will be most successful when employed by providers with whom patients have a high level of trust and a good therapeutic alliance.

There are several strengths of our study. This is the first quantitative study regarding the effect of the patient-provider relationship quality on fracture prevention medication persistence, adjusting for other variables that have been shown to be strongly associated with medication persistence and compliance. This is also the first study to address the association between the patient-provider relationship quality and other predictors of fracture prevention medication persistence (most notably medication attitudes held by the patient), allowing us to hypothesize and test the mechanisms by which the patient-provider relationship can be leveraged to improve fracture prevention medication persistence. This is also the first study of fracture prevention medication compliance to include objective measures of fracture risk from the medical record, most notably bone mineral density. Our response rate of 63%, while not excellent, is nonetheless much better than some others that have assessed the association between attitudes regarding fracture prevention medications and persistence with those medications.

There are also important limitations of this study. We had to use self-report to assess medication persistence because we did not have access to pharmacy claims data for most of the cohort. This study is cross-sectional, and hence the study is

subject to recall bias on the part of patients with respect to their medication use behavior. Because our sampling frame included only those who had one or more prescriptions for an oral bisphosphonate recorded in the medical record, our study sample did not include any patients who refused to accept a prescription for a fracture prevention medication from the outset.

To conclude, the quality of the patient-provider relationship from the patient's perspective is modestly associated with self-reported persistence with fracture prevention medication. Providers who have a better relationship with their patients at high risk of fracture may be better able to influence those patients' perceived need for fracture prevention medication, alleviate concerns about the long-term safety of and dependence upon those medications, and influence medication use self-efficacy, and thereby positively influence persistence with fracture prevention medication. Further research is needed regarding the actual content of conversations that providers have with their patients when recommending fracture prevention therapy, and how that content can be altered to maximally leverage the trust that patient's have in their providers to improve appropriate persistence with fracture prevention medication.

Table 5-1: Parameter Estimates Instrumental Variables Analyses

Instrumented Variable(s)	Perceived Need for Medication	Concerns about Medication	Wald Test * (p-value)
None (95% C.I.)**	-0.37 (-0.49 to -0.26)	0.11 (0.00 to 0.22)	
Perceived Need for Medication Only	-0.39 (-0.81 to 0.02)	0.14 (-0.05 to 0.33)	0.01 (p = 0.91)
Perceived Need & Concerns about Medications	-0.43 (-0.87 to 0.01)	0.03 (-0.34 to 0.39)	0.24 (p = 0.89)

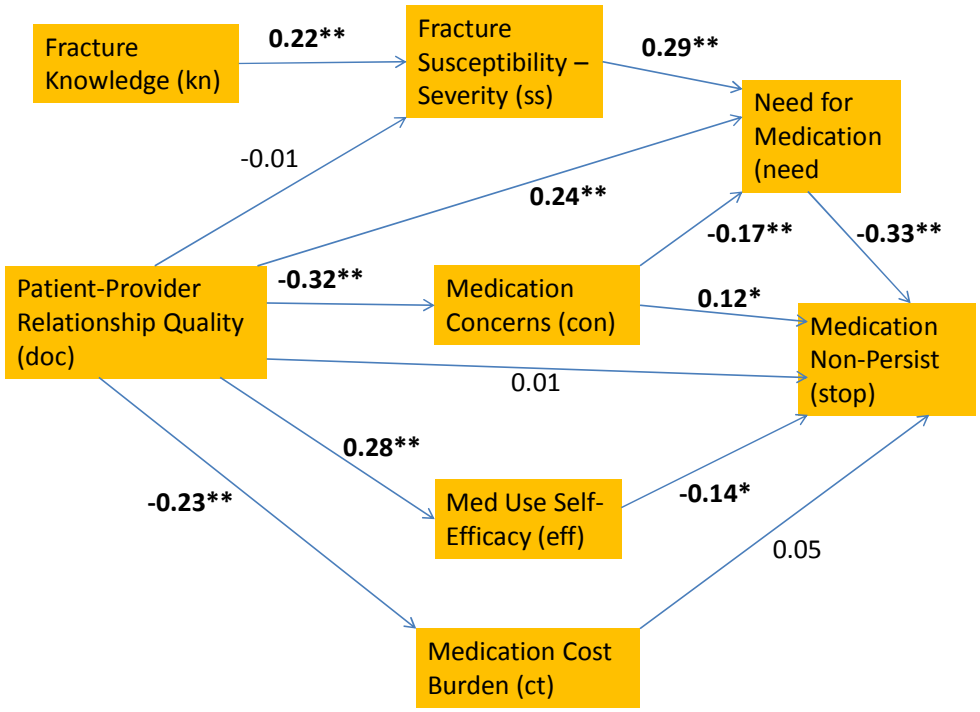
***Test for significant regression error term correlations
**All Predictors treated as exogenous variables

Table 5-2: Attenuation of the Effect of the Patient-Provider Relationship Quality on Non-Persistence by Addition of Postulated Mediating Variables

Mediating Predictors Included	Standardized Parameter Estimate for Patient-Provider Relationship Quality* (95% C.I.)
Base (no additional mediators)*	-0.158 (-0.261 to -0.056)
Base plus *Perceived Need for Fracture Prevention Medication*	-0.080 (-0.189 to 0.028)
Base plus *Medication Concerns* & Perceived Need for Fracture Prevention Medication	-0.044 (-0.156 to 0.070)
Base plus *Med Use Self-Efficacy*, Medication Concerns, & Perceived Need for Fracture Prevention Medication	-0.024 (-0.139 to 0.091)
Base plus *Medication Cost Burden*, Med Use Self-Efficacy, Medication Concerns, & Perceived Need for Fracture Prevention Medication	-0.016 (-0.132 to 0.100)

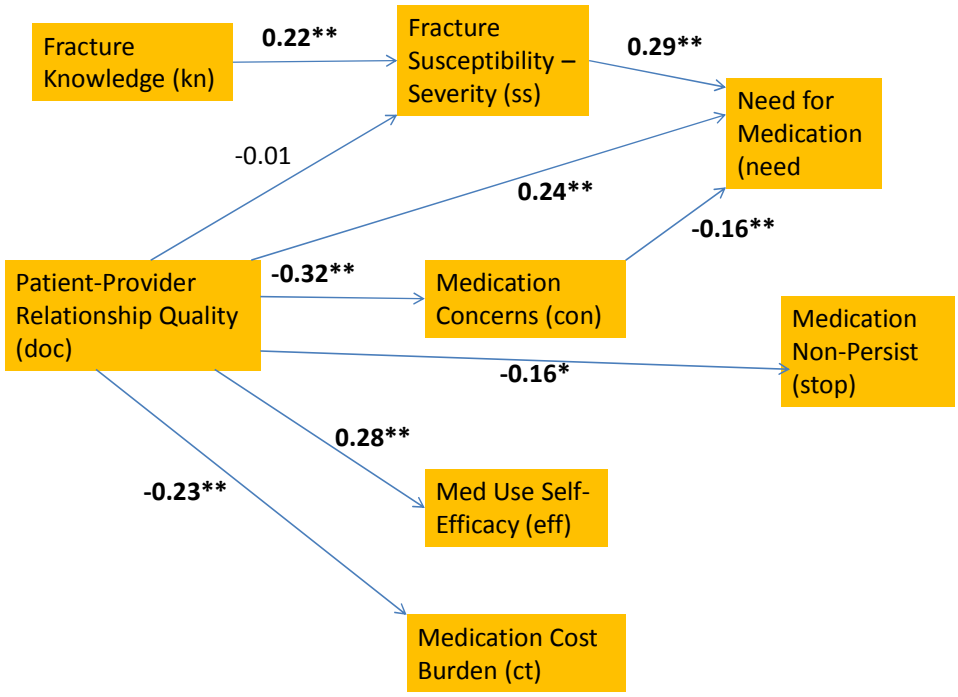
*Adjusted for proton pump inhibitor use, number of adverse drug reactions in medical record, depression, personal history of fracture, family history of fracture, bone mineral density T-score, age, educational level, income level, smoking status, glucocorticoid use, and prevalent vertebral fracture status on VFA

Figure 5-1: Effects of Patient-Provider Relationship Quality (Full Path Model, Standardized Parameter Estimates)



*Parameter estimates that are significantly different from zero at a p-value <0.05
**Parameter estimates that are significant at p-value <0.0001 (also in bold)

Figure 5-2: Effects of Patient-Provider Relationship Quality (Restricted Path Model, Standardized Parameter Estimates)



Chapter 6

Conclusions

As the overall disease burden in the population of industrialized and industrializing countries continues to shift increasingly to chronic diseases for which their management requires the long-term use of medication,(316-318) non-compliance with those medications is important.(319) Non-compliance to anti-hypertensive medication is associated with lack of blood pressure control which in turn is associated increased incidence of morbid and fatal cardiovascular disease events,(320) and non-compliance with oral medications to control blood glucose and anti-hypertensive medications with increased hospitalization, health care utilization, and health care costs.(321) Non-compliance with anti-retroviral medications is associated with higher viral load among patients with HIV infection,(147) which in turn is associated with increased immunodeficiency, infections, and mortality. Non-compliance with fracture prevention medication among that subset of older individuals at high risk of fracture is associated with higher rates of fractures and higher health care costs.(34, 44, 59-61, 63, 65, 322)

When medication use behavior is conceptualized as purposeful, goal-directed behavior, then the attitudes that individuals who are prescribed medication have of both the consequences of the target condition and of the medications themselves are important in their decisions as to whether or not to accept a prescription to treat a chronic condition and persist with it.(276, 278, 284) This study has confirmed that the necessity-concerns framework, which has been used with moderate success predict medication use behavior in other chronic illnesses such as asthma,(145, 292) HIV infection,(146, 147) diabetes mellitus,(143, 237) and cardiovascular disease,(143, 237) is also a reasonable conceptual framework with which to explain use of fracture prevention medication use behavior.

Summary of Principal Findings of this Project

This work extends substantially previous formulations of the necessity-concerns framework in general, identifies additional predictors that in the context of the necessity-concerns framework are important for understanding fracture prevention medication use, and extends understanding of medication use behavior in several ways.

Predictors of Non-Persistence Compared to Non-Compliance

This study strongly suggests that non-persistence, that is failing to maintain use of a medication for the duration of time for which it was prescribed, has a different (although overlapping) set of predictors than compliance, defined broadly by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as taking medication in the correct doses at the correct time. Persistence with fracture prevention medication was strongly associated with perceived need for fracture prevention medication, modestly with concerns about the long term safety of and dependence upon medication, and with medication use self-efficacy. Although age appeared to be have a direct negative association with non-persistence, age also was negatively associated with perceived need for fracture prevention medication, a paradoxical result given that fracture risk rises with age. The indirect association of age through perceived need for medication with non-persistence therefore was positive, and hence the *total* effect of age with either aspect of non-persistence was insignificant.

In contrast, self-reported non-compliance (defined more narrowly as missing prescribed doses) was associated moderately strongly with medication use self-efficacy and concerns about the long-term risks of and dependence upon medications, but was not associated with perceived need for medication. The former association suggests that some missed doses are unintentional, but the latter association suggests that some missed doses may be intentional to reduce one's sense of risk from or dependence upon medication use. Those of older age self-reported less non-compliance than those of younger age, and this effect was nearly entirely direct and not through any other predictors.

Predictors of Non-Persistence due to Side Effects Compared to Non-Persistence for Other Reasons

Non-persistence can also be conceptualized as due to side effects or due to other reasons, and these also have an overlapping but different set of predictors. Perceived need for fracture prevention medication is an important predictor of both. Concerns about the long-term safe of and dependence upon medications, however, is primarily associated with discontinuation of medication due to side effects, and less so with discontinuation for other reasons. Consistent with this, bad experiences with

medications, operationally defined as the number of adverse drug reactions listed in the ADR file of the medical record, is also associated with non-persistence due to side effects but not with non-persistence for other reasons. These results are consistent with the hypothesis that those with adverse events while on medication are more likely to attribute causality for those events to one or more medications that they are taking and/or perceive a greater threat to their health from those events if they have substantial concerns about the long-term safety of these medications or have had prior bad experiences with medication. Finally, PPI use was associated with non-persistence due to side effects , an expected finding since PPI's are used to treat gastric acidity disorders and dyspepsia is the most common side effect to oral bisphosphonate medication. PPI use was not associated with non-persistence for reasons other than side effects or with non-compliance.

In contrast, medication use self-efficacy was associated with non-persistence for reasons other than side effects but not significantly with non-persistence due to side effects. Perceived medication cost burden was mildly associated with non-persistence for other reasons and not at all with non-persistence due to side effects, consistent with other work that generally shows that perceived medication cost burden appears to be a predictor of medication use behavior only among those of limited income. Current or past smoking was associated with non-persistence for reasons other than side effects compared never having been a smoker, but not with non-persistence due to side effects. The reasons for this are unclear, especially since this association was independent of the four main medication attitude variables.

Predictors of Perceived Need for Fracture Prevention Medication

This study is the first among those using the necessity-concerns framework that has examined predictors of perceived need for medication. As expected, perceived need for fracture prevention medication is associated with perceived susceptibility to and severity (health consequences) of fractures, with the quality of the patient-provider relationship quality, and mildly with concerns about medications. Among objective indicators of fracture risk, documented prevalent vertebral fracture on lateral spine imaging done on a bone density has the strongest association with perceived need for fracture prevention medication, but unexpectedly this effect is direct rather than through perceived fracture susceptibility*severity. Moreover, the effect of bone mineral

density on perceived need for fracture prevention medication is weak. Although personal history and family history of fracture are mildly associated with fracture susceptibility*severity, their associations (direct plus indirect) on perceived need for medication are insignificant. Fracture knowledge has a weak indirect association with perceived need for fracture prevention medication. Through perceived need for fracture prevention medication, the presence of a prevalent vertebral fracture on lateral densitometric spine imaging and lower bone mineral density had, respectively, modest and weak effects on medication persistence.

The effect of the quality of the patient-provider relationship quality on medication use behavior

Many studies have shown that patient satisfaction with medical care and with the providers of that care are associated with the trust that the patient has in that provider to provide competent care, to consider patient's interests paramount, how well they communicate with and answer patient's concerns, and how congruent their decision making style is with the patient's. Only a few studies have evaluated the association of these variables specifically with medication non-persistence and non-compliance, and none to date have estimated the association of the patient-provider relationship quality with medication attitudes, or whether or not these medication attitudes mediate the association between medication use behavior and the patient-provider relationship quality.

While the component scales in the patient-provider relationship quality construct were developed as separate scales, this study suggests that trust in the provider, perceived openness of provider communication, and congruence with provider decision making style are all part of the same construct. In this study, the patient-provider relationship quality was modestly associated with medication non-persistence, and roughly half of the effect was through perceived need for fracture prevention medication and about 25% through medication concerns, and most of the remainder through medication use self-efficacy, with little if any direct effect on non-persistence. However, no association between the patient-provider relationship quality and perceived fracture susceptibility*severity was evident in this dataset. While this could mean that providers influence on their patients' perceptions of their fracture susceptibility*severity is unrelated to the patient-provider relationship quality, it is more

likely that providers are not leveraging the trust that their patients' do have in them to improve the congruence between their actual fracture risk and their perceived fracture susceptibility*severity and need for fracture prevention medication.

Better Estimation of the Total Effects of Predictor Variables with Multivariate Models

A key difference between this study of medication use behavior and prior ones is that, with one exception,(145) prior studies have used single-equation regression models to estimate the association of predictors with use of fracture prevention medication. The overall effect of certain predictors on medication use behavior, however, may be over or underestimated because indirect effects through other predictors are missed. For example, one-third of the association between concerns about medications and non-persistence with fracture prevention medication was indirect through perceived need for fracture prevention medication. Similarly, the association between the patient-provider relationship quality and medication non-persistence would be judged to be insignificant if this had been estimated with a single-equation model with the medication attitudes included as covariates.

Implications of Project Findings

The results of this project have several implications with respect to improving medication compliance with fracture prevention medications in particular and with compliance with chronic medication to prevent adverse future health outcomes in general. First, vertebral fracture assessment may have a significant role to play in encouraging compliance among fracture prevention medication. Two-thirds to three-quarters of vertebral fractures occur without acute clinical symptoms, and generally are unrecognized clinically until lateral spine imaging reveals their presence.(323, 324) They are a marker of skeletal fragility, and those with one or more prevalent vertebral fractures have a four-fold higher incidence of vertebral fracture and a two-fold higher incidence of hip fracture compared to those without prevalent vertebral fracture, adjusted for age and bone mineral density.(294, 296, 325-327) Moreover, prevalent vertebral fractures are common among older women and men; the population-based prevalence of moderate to severe vertebral fracture among women in Rochester, Minnesota age 70 to 74 has been estimate to be 21%.(328) In the European Vertebral

Osteoporosis Study, the age-adjusted prevalence of vertebral fracture among both women and men age 50 and older were 12% to 20%, depending on the method of vertebral fracture adjudication used.(329) More widespread use of vertebral fracture may therefore identify a significant subset of older men and women who not only are at higher risk of fracture, but also by virtue of having that prevalent vertebral fracture identified have a higher perceived need for fracture prevention medication. In this way, vertebral fracture assessment may modestly improve fracture prevention compliance among the subset of older women and men who are at the highest risk of fracture, and for which the efficacy of fracture prevention medication has been most extensively established.

Second, the constellation of variables that influence medication use behavior is complex and varies from person to person. Therefore, simple interventions such as provision of education materials or follow-up phone calls to encourage patients by and large have not been effective in improving medication compliance, and only complex interventions that employ a variety of interventions including encouraging self-monitoring, increasing convenience of medication use, education, and telephone follow-up, often delivered by multidisciplinary teams that are not easy to translate into clinical practice, have had a measureable effect on medication use behavior.(330-333) Moreover, the extent to which these studies have assessed medication and target condition attitudes and have tailored the intervention accordingly is unclear. The results of this project confirm that attitudes regarding medications are important predictors of chronic medication use behavior, and suggest that interventions to improve compliance will be limited if patients' attitudes regarding medications recommended to them are not solicited and addressed. In particular, providers may be able to influence positively appropriate medication use behavior by assessing the congruence of patients' perceived need for fracture prevention medication with their actual fracture risk, personal priorities and values, by eliciting and addressing concerns they may have regarding the long-term safety of and dependence upon medications, and assessing their confidence in taking medication in the context of their daily lives. However, the lack of any association between the patient-provider relationship quality and patient perceived fracture susceptibility*severity, and the weak associations between objective indicators of fracture prevention medication and perceived need for fracture prevention

medication suggests that providers may not be adequately engaging with patients as to why they *personally* are at high risk of fracture.

However, providers do not appear to have the time or resources within the context of traditional organization of clinical practice to perform these assessments for their patients treated for chronic illnesses. A recent study of videotaped interactions between primary care providers and patients for whom they were prescribing a new medication showed that providers discussed the side effects of the proposed new drug only 35% of the time,(297) let alone the more time consuming tasks of assessing the patient's attitudes toward the target condition being treated, the medication proposed to treat that target condition, and patient concerns about medications in general. Clinical primary care practice has traditionally been organized to treat acute episodes of illness rather than manage chronic conditions, and there has been considerable concern that current reimbursement policies for medical care rendered for Medicare beneficiaries creates disincentives to engage with patients with chronic illnesses adequately regarding the medications used to manage these illnesses.(318, 334) In particular, elicitation of patient preferences and values regarding treatment options may require more time. Discussions focused on patient attitudes regarding the target condition(s) and the medications proposed to treat them would naturally include elicitation of patient preferences and values.(335)

Over the last two decades, conceptual frameworks of chronic care management such as the Chronic Care Model and the Medical Home have been developed to better address the needs of patients with chronic illnesses or complex care needs.(336-338) The Chronic Care Model emphasizes not only disease management techniques, but also improving self-management of chronic conditions by patients themselves, providing decision support (both in the form of evidence-based guidelines for use by providers and decision aids to help patients choose among options for managing a particular medical problem), and information systems to coordinate care among different providers.(339) One particular application of the Chronic Care Model, Guided Care, is intended to improve quality of care and health outcomes among elderly individuals with multiple co-morbidities.(340, 341) This approach utilizes trained nurses to develop a Care Guide in conjunction with the patient's primary care provider from an assessment of the patient's medical, functional, and psychosocial status and evidence-base guidelines. The Guided Care Nurse is

trained to use motivational interviewing techniques to identify patient goals and preferences, and to motivate the patient to actively participate in his or her care and adhere to the Care Guide.(340) It is in the context of this function that the Guided Care Nurse could elicit patients' medication attitudes, addressing misconceptions regarding these medications and the target conditions they are intended to treat, and putting together a medication use and monitoring plan to reduce the risk of harm and improve patients' medication use self-efficacy. An advantage of this approach is that the Guided Care Nurse works with a small group of primary care providers, but the overall structure of the primary care practice requires little alteration.

Limitations of This Project

There are several important limitations to this project. First, as discussed in the chapters within which the results of this project are presented, is the use of self-report to assess medication use behavior. The accuracy of self-report for medication use is only modest, and it generally is biased in favor of over-reporting compliance and persistence. This biases our estimated associations of predictors with medication use behavior toward the null, and hence some of the associations that we found to be insignificant might appear to have a modest association with medication use behavior if a more accurate measure of medication use were employed.

Second, the cross-sectional design of this study leaves open the possibility that reverse causality may bias some of our findings. For example, if an individual discontinues oral bisphosphonate medication and subsequently experiences no fractures for several months (especially if they had a fall and did not fracture) they may conclude that fracture prevention medication is not as important for their health as they might have otherwise thought. Similarly, if a person unintentionally forgets to take medication or in the context of their task environment does not get a medication refilled, their medication use self-efficacy may erode from this. These reverse causal pathways, if present, would exaggerate the association between medication use behavior and some of its purported predictors. While it is true that the instrumental variables (IV) analyses did not reveal substantial changes in the estimated associations between medication use behavior either perceived need for or concerns about medication, the confidence intervals around the IV parameter estimates are wide, and hence the IV analyses cannot fully rule out this source of bias.

Third, there are several potential predictors of medication use that we did not assess as part of this project, and their exclusion may account for some of the unexplained variance in medication use and other dependent variables in the empirical model. First, we did not assess *health value*, that is how salient health is for the participants in this study. The salience of health refers to the degree to which individuals make preserving their health a priority among the competing demands on their time and cognitive resources.(342) While some may have maintenance of their health as one of their top priorities, others may rank other needs higher (such as their job, maintaining their home, or attending to the health or needs of others within their family or close social network). Low relative health value could explain why some individuals might not comply with medication use in spite of being at high risk of fracture.

Related to health salience, we did not assess time preference. *Positive time preference* refers to the extent to which individuals devalue costs and benefits that may be borne or accrue in the future compared to present day costs and benefits.(343, 344) That is, delayed gratification is of less value in varying degrees to humans than immediate gratification. This is of relevance to medication use to prevent adverse consequences of chronic illness in general and osteoporotic fracture in particular, because in essence when a patient is prescribed a preventive medication they are being asked to expend resources (cognitive and financial) in the present day to prevent events that may or may not happen in the future. Those with a highly positive time preference may be significantly less willing to take on preventive health behaviors particularly if these interfere with other activities that yield immediate rewards. Empiric studies suggest that individuals' time preferences with respect to health benefits and costs are variable and may influence their health behaviors,(345-347) with those who discount future health benefits to a greater degree being less willing to expend present-day resources to gain delayed health benefits, which may then lead to adverse future health outcomes.(348)

Finally, we did not assess the influence of participants' social network ties, be they strong ties (such as family members and close friends) or weak ties (such as internet web sites or direct-to-consumer advertising). There is a large literature that has documented the influence of close social network ties and of ethnicity-related social norms on health beliefs and on perceived value of certain classes of interventions,(349,

350) be they allopathic interventions, complementary and alternative medicine interventions, or self-help interventions.(196, 200, 351) Attitudes toward medications specifically have been shown to be related to ethnicity,(352) and are highly likely to be influenced by one's social network. Similarly, while the ultimate effect of direct- to-consumer pharmaceutical advertising on actual medication use behavior is still under debate, there is strong evidence that these advertisements do stimulate patients and their families to investigate these products and engage in conversations with their health care providers regarding their possible use.(353, 354) The omission of these variables may again be responsible for some of the unexplained variance of self-reported medication use behavior in this project.

Future Research Agenda

The unimpressive changes in medication use behavior to treat chronic illness that have been seen in interventional studies to improve compliance with medication to treat a variety of chronic illnesses raises the issue of whether or not these have failed in part due to an incomplete understanding of the phenomenon of medication use behavior. An extant question from this project is whether or not an interventional study is worthy of pursuit now based on the findings presented in this thesis, or whether further study of predictors of the underlying phenomenon is needed first. On one hand, it appears that the studies of interventions to improve compliance have focused primarily on medication use self-efficacy, dosing convenience, follow-up phone support, and general education about the target intervention, and it is unclear that the interventions adequately engaged participants about their medication and target condition beliefs in an interactive manner. On the other hand, as has been outlined throughout this thesis, there remains much to be learned about the determinants of medication use behavior.

It may be possible to devise an intervention study employing motivational interviewing to help patient's articulate their priorities and values, identify and correct misconceptions about the target condition and the medications proposed to treat them, devise a management protocol including medication use that is safe from the patient's perspective, and point out ways in which *not* using medication is adverse to their priorities, values, and goals. Done prospectively, such a study could employ a hierarchical (since patients will be nested within providers and clinics) panel data

design, where medication use behavior over one time period is included as a predictor for medication use behavior at subsequent time periods.

However, several additional components would be critical to include. First, such a study should be done in settings where there is complete access to pharmacy claims data, both because pharmacy claims are more accurate than self-report, and because once an individual has given consent at the start of the study, the dependent variable can be quietly assessed in the background minimizing the degree to which the assessment of medication compliance itself influences medication use behavior. Second, this study should be done in the context of a care system that can reliably deliver a meaningful intervention, such as one employing many facets of the chronic care model, and not in a health care setting focused only or even primarily on short-term acute health care needs. Third, health salience, time preference and social network influences should be included as covariates (at least at baseline) in addition to the other predictors demonstrated to be of importance in this project. Such a study likely will require additional preliminary work to develop good measures of time preference and social network influences specifically around the issue of medication attitudes and use.

References

1. **Cramer JA, Roy A, Burrell A, et al.** Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11(1):44-7.
2. **Rosen CJ.** Pathogenesis of osteoporosis. *Baillieres Best Pract Res Clin Endocrinol Metab*. 2000;14(2):181-93.
3. **Raisz LG.** Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest*. 2005;115(12):3318-25.
4. **Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL.** Perspective: how many women have osteoporosis? *Journal of Bone and Mineral Research*. 1992;7:1005-1010.
5. **Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE.** Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J Gerontol*. 1990;45(3):M101-7.
6. **Hannan EL, Magaziner J, Wang JJ, et al.** Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. *Jama*. 2001;285(21):2736-42.
7. **Fink HA, Ensrud KE, Nelson DB, et al.** Disability after clinical fracture in postmenopausal women with low bone density: the fracture intervention trial (FIT). *Osteoporos Int*. 2003;14(1):69-76.
8. **Nevitt MC, Ettinger B, Black DM, et al.** The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med*. 1998;128(10):793-800.
9. **Huang C, Ross PD, Wasnich RD.** Vertebral fractures and other predictors of back pain among older women. *J Bone Miner Res*. 1996;11(7):1026-32.
10. **Culham EG, Jimenez HA, King CE.** Thoracic kyphosis, rib mobility, and lung volumes in normal women and women with osteoporosis. *Spine*. 1994;19(11):1250-5.
11. **Lombardi I, Jr., Oliveira LM, Mayer AF, Jardim JR, Natour J.** Evaluation of pulmonary function and quality of life in women with osteoporosis. *Osteoporos Int*. 2005;16(10):1247-53.
12. **Schlaich C, Minne HW, Bruckner T, et al.** Reduced pulmonary function in patients with spinal osteoporotic fractures. *Osteoporos Int*. 1998;8(3):261-7.
13. **Hochberg MC, Thompson DE, Black DM, et al.** Effect of alendronate on the age-specific incidence of symptomatic osteoporotic fractures. *J Bone Miner Res*. 2005;20(6):971-6.
14. **McClung MR, Geusens P, Miller PD, et al.** Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*. 2001;344(5):333-40.
15. **Cummings SR, Black DM, Thompson DE, et al.** Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *Jama*. 1998;280(24):2077-82.
16. **Cranney A, Tugwell P, Zytaruk N, et al.** Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev*. 2002;23(4):524-8.

17. **Cranney A, Tugwell P, Adachi J, et al.** Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev*. 2002;23(4):517-23.
18. **Hodgson SF, Watts NB, Bilezikian JP, et al.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. *Endocr Pract*. 2003;9(6):544-64.
19. **ACOG CoP.** ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Osteoporosis. Number 50, January 2003. *Obstet Gynecol*. 2004;103(1):203-16.
20. **Brown JP, Josse RG.** 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Cmaj*. 2002;167(10 Suppl):S1-34.
21. **Foundation NO.** Physician guide to prevention and treatment of osteoporosis. Vol. 2005; 2003.
22. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama*. 2002;288(3):321-33.
23. **Ettinger B, Black DM, Mitlak BH, et al.** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637-45.
24. **Lowry KP, Dudley TK, Oddone EZ, Bosworth HB.** Intentional and unintentional noncompliance to antihypertensive medication. *Ann Pharmacother*. 2005;39(7-8):1198-203.
25. **Burnier M.** Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. *Blood Press Monit*. 2000;5 Suppl 1:S31-4.
26. **Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J.** Long-term persistence in use of statin therapy in elderly patients. *Jama*. 2002;288(4):455-61.
27. **Jackevicius CA, Mamdani M, Tu JV.** Compliance with statin therapy in elderly patients with and without acute coronary syndromes. *Jama*. 2002;288(4):462-7.
28. **Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ.** Systematic review and meta-analysis of real-world compliance to drug therapy for osteoporosis. *Mayo Clin Proc*. 2007;82(12):1493-501.
29. **Cramer JA, Gold DT, Silverman SL, Lewiecki EM.** A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007;18(8):1023-31.
30. **Blouin J, Dragomir A, Ste-Marie LG, Fernandes JC, Perreault S.** Discontinuation of antiresorptive therapies: a comparison between 1998-2001 and 2002-2004 among osteoporotic women. *J Clin Endocrinol Metab*. 2007;92(3):887-94.

31. **Cramer JA, Amonkar MM, Hebborn A, Altman R.** Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin*. 2005;21(9):1453-60.
32. **Ettinger MP, Gallagher R, MacCosbe PE.** Medication persistence with weekly versus daily doses of orally administered bisphosphonates. *Endocr Pract*. 2006;12(5):522-8.
33. **Gold DT, Martin BC, Frytak JR, Amonkar MM, Cosman F.** A claims database analysis of persistence with alendronate therapy and fracture risk in post-menopausal women with osteoporosis. *Curr Med Res Opin*. 2007;23(3):585-94.
34. **Huybrechts KF, Ishak KJ, Caro JJ.** Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. *Bone*. 2006;38(6):922-8.
35. **Lo JC, Pressman AR, Omar MA, Ettinger B.** Persistence with weekly alendronate therapy among postmenopausal women. *Osteoporos Int*. 2006;17(6):922-8.
36. **Papaioannou A, Ioannidis G, Adachi JD, et al.** Compliance to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database. *Osteoporos Int*. 2003;14(10):808-13.
37. **Solomon DH, Avorn J, Katz JN, et al.** Compliance with osteoporosis medications. *Arch Intern Med*. 2005;165(20):2414-9.
38. **Recker RR, Gallagher R, MacCosbe PE.** Effect of dosing frequency on bisphosphonate medication compliance in a large longitudinal cohort of women. *Mayo Clin Proc*. 2005;80(7):856-61.
39. **Cooper A, Drake J, Brankin E.** Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract*. 2006;60(8):896-905.
40. **Weiss TW, Henderson SC, McHorney CA, Cramer JA.** Persistence across weekly and monthly bisphosphonates: analysis of US retail pharmacy prescription refills. *Curr Med Res Opin*. 2007;23(9):2193-203.
41. **McHorney CA, Schousboe JT, Cline RR, Weiss TW.** The impact of osteoporosis medication beliefs and side-effect experiences on non-compliance to oral bisphosphonates. *Curr Med Res Opin*. 2007;23(12):3137-52.
42. **Briesacher BA, Andrade SE, Fouayzi H, Chan KA.** Comparison of drug compliance rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008;28(4):437-43.
43. **Jones TJ, Petrella RJ, Crilly R.** Determinants of persistence with weekly bisphosphonates in patients with osteoporosis. *J Rheumatol*. 2008;35(9):1865-73.
44. **McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J.** Compliance with drug therapies for the treatment and prevention of osteoporosis. *Maturitas*. 2004;48(3):271-87.
45. **Penning-van Beest FJ, Erkens JA, Olson M, Herings RM.** Determinants of non-compliance with bisphosphonates in women with postmenopausal osteoporosis. *Curr Med Res Opin*. 2008;24(5):1337-44.

46. **Downey TW, Foltz SH, Boccuzzi SJ, Omar MA, Kahler KH.** Compliance and persistence associated with the pharmacologic treatment of osteoporosis in a managed care setting. *South Med J*. 2006;99(6):570-5.
47. **Zambon A, Baio G, Mazzaglia G, Merlino L, Corrao G.** Discontinuity and failures of therapy with bisphosphonates: joint assessment of predictors with multi-state models. *Pharmacoepidemiol Drug Saf*. 2008;17(3):260-9.
48. **Zafran N, Liss Z, Peled R, Sherf M, Reuveni H.** Incidence and causes for failure of treatment of women with proven osteoporosis. *Osteoporos Int*. 2005;16(11):1375-83.
49. **Berecki-Gisolf J, Hockey R, Dobson A.** Compliance to bisphosphonate treatment by elderly women. *Menopause*. 2008;15(5):984-90.
50. **Turbi C, Herrero-Beaumont G, Acebes JC, et al.** Compliance and satisfaction with raloxifene versus alendronate for the treatment of postmenopausal osteoporosis in clinical practice: An open-label, prospective, nonrandomized, observational study. *Clin Ther*. 2004;26(2):245-56.
51. **Morisky DE, Green LW, Levine DM.** Concurrent and predictive validity of a self-reported measure of medication compliance. *Med Care*. 1986;24(1):67-74.
52. **Guilera M, Fuentes M, Grifols M, Ferrer J, Badia X.** Does an educational leaflet improve self-reported compliance to therapy in osteoporosis? The OPTIMA study. *Osteoporos Int*. 2006;17(5):664-71.
53. **Carnevale V, Nieddu L, Romagnoli E, et al.** Osteoporosis intervention in ambulatory patients with previous hip fracture: a multicentric, nationwide Italian survey. *Osteoporos Int*. 2006;17(3):478-83.
54. **Tosteson AN, Grove MR, Hammond CS, et al.** Early discontinuation of treatment for osteoporosis. *Am J Med*. 2003;115(3):209-16.
55. **Hamilton B, McCoy K, Taggart H.** Tolerability and compliance with risedronate in clinical practice. *Osteoporos Int*. 2003;14(3):259-62.
56. **Pickney CS, Arnason JA.** Correlation between patient recall of bone densitometry results and subsequent treatment compliance. *Osteoporos Int*. 2005;16(9):1156-60.
57. **Rossini M, Bianchi G, Di Munno O, et al.** Determinants of compliance to osteoporosis treatment in clinical practice. *Osteoporos Int*. 2006;17(6):914-21.
58. **Cline RR, Farley JF, Hansen RA, Schommer JC.** Osteoporosis beliefs and antiresorptive medication use. *Maturitas*. 2005;50(3):196-208.
59. **Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C.** The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int*. 2004;15(12):1003-8.
60. **Briesacher BA, Andrade SE, Yood RA, Kahler KH.** Consequences of poor compliance with bisphosphonates. *Bone*. 2007;41(5):882-7.
61. **Penning-van Beest FJ, Erkens JA, Olson M, Herings RM.** Loss of treatment benefit due to low compliance with bisphosphonate therapy. *Osteoporos Int*. 2008;19(4):511-7.
62. **Reginster JY.** Compliance and persistence: impact on outcomes and health care resources. *Bone*. 2006;38(2 Suppl 2):S18-21.

63. **Siris ES, Harris ST, Rosen CJ, et al.** Compliance to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc*. 2006;81(8):1013-22.
64. **Sunyecz JA, Mucha L, Baser O, Barr CE, Amonkar MM.** Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization. *Osteoporos Int*. 2008;19(10):1421-9.
65. **Rabenda V, Mertens R, Fabri V, et al.** Compliance to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int*. 2008;19(6):811-8.
66. **Newell A.** Unified Theories of Cognition. Cambridge, MA: Harvard University Press; 1990.
67. **Simon H.** *The Sciences of the Artificial* Cambridge, MA: The MIT Press; 1996.
68. **Gigerenzer G, Todd PM.** *Simple Heuristics that Make Us Smart* New York: Oxford University Press; 1999.
69. **Tversky A, Kahneman D.** Availability: a heuristic for judging frequency and probability. *Cognitive Psychology*. 1973;5:207-232.
70. **Tversky A, Kahneman D.** Judgment under uncertainty: heuristics and biases. *Science*. 1974;185:1124-1131.
71. **Schwarz N, Vaughn LA.** The Availability heuristic revisited: ease of recall and content of recall as distinct sources of information. In: Gilovich T, Griffin D, Kahneman D, eds. *Heuristics and Biases. The Psychology of Intuitive Judgment*. New York: Cambridge University Press; 2002:103-119.
72. **Maio GR, Olson JM, Bernard MM, Luke MA.** Ideologies, Values, Attitudes, and Behavior. In: Delamater J, ed. *Handbook of Social Psychology*. New York: Kluwer Academic / Plenum Publishers; 2003:283-308.
73. **Maio GR, Olson JM.** Relations between Values, Attitudes, and Behavioral Intentions: the Moderating Role of Attitude Function. *Journal of Experimental Social Psychology*. 1995;31:266-285.
74. **Oskamp S, Schultz PW.** *Attitudes and Opinions*. 3rd ed Mahwah, NJ: Lawrence Erlbaum Associates; 2005.
75. **Pratkanis AR, Greenwald AG.** A Sociocognitive Model of Attitude Structure and Function. *Advance in Experimental and Social Psychology*. 1989;22:245-285.
76. **Echabe AE, Guillen CS, Ozamiz JA.** Representations of health, illness, and medicines. Coping strategies and health-promoting behavior. *Br J Social Psychol*. 1992;31:339-349.
77. **Donovan J, Blake D.** Patient non-compliance: deviance or reasoned decision making? *Social Science and Medicine*. 1992;34(5):507-513.
78. **Trostle J.** The History and Meaning of Patient Compliance as an Ideology. In: Gochman DS, ed. *Handbook of Health Behavior Research II. Provider Determinants*. New York: Plenum Press; 1997:109-124.
79. **Hausman A.** Taking your medicine: relational steps to improving patient compliance. *Health Mark Q*. 2001;19(2):49-71.

80. **Heisler M, Bouknight RR, Hayward RA, Smith DM, Kerr EA.** The relative importance of physician communication, participatory decision making, and patient understanding in diabetes self-management. *J Gen Intern Med*. 2002;17(4):243-52.
81. **Charles C, Gafni A, Whelan T.** Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. *Soc Sci Med*. 1999;49(5):651-61.
82. **Federman AD, Cook EF, Phillips RS, et al.** Intention to discontinue care among primary care patients: influence of physician behavior and process of care. *J Gen Intern Med*. 2001;16(10):668-74.
83. **Lupton D.** Consumerism, reflexivity and the medical encounter. *Soc Sci Med*. 1997;45(3):373-81.
84. **Jahng KH, Martin LR, Golin CE, DiMatteo MR.** Preferences for medical collaboration: patient-physician congruence and patient outcomes. *Patient Educ Couns*. 2005;57(3):308-14.
85. **DiMatteo MR, Sherbourne CD, Hays RD, et al.** Physicians' characteristics influence patients' compliance to medical treatment: results from the Medical Outcomes Study. *Health Psychol*. 1993;12(2):93-102.
86. **Kaplan SH, Gandek B, Greenfield S, Rogers W, Ware JE.** Patient and visit characteristics related to physicians' participatory decision-making style. Results from the Medical Outcomes Study. *Med Care*. 1995;33(12):1176-87.
87. **Anderson LA, Dedrick RF.** Development of the Trust in Physician scale: a measure to assess interpersonal trust in patient-physician relationships. *Psychol Rep*. 1990;67(3 Pt 2):1091-100.
88. **Thom DH, Ribisl KM, Stewart AL, Luke DA.** Further validation and reliability testing of the Trust in Physician Scale. The Stanford Trust Study Physicians. *Med Care*. 1999;37(5):510-7.
89. **Hall MA, Dugan E, Zheng B, Mishra AK.** Trust in physicians and medical institutions: what is it, can it be measured, and does it matter? *Milbank Q*. 2001;79(4):613-39, v.
90. **Janz N, Becker M.** The Health Belief Model: a decade later. *Health Education Quarterly*. 1984;11(1):1-47.
91. **Rosenstock IM, Strecher VJ, Becker MH.** Social learning theory and the Health Belief Model. *Health Educ Q*. 1988;15(2):175-83.
92. **Sheeran P, Abraham C.** The Health Belief Model. In: Connor M, Norman P, eds. *Predicting Health Behavior*. Philadelphia: Open University Press; 1995:23-61.
93. **Leventhal H, Diefenbach M, Leventhal EA.** Illness cognition: using common sense to understand treatment compliance and affect cognitive interactions. *Cognitive Therapy and Research*. 1992;16(2):143-163.
94. **Ajzen I.** The Theory of Planned Behavior. *Organizational Behavior and Human Decision Processes*. 1991;50:179-211.
95. **Connor M, Sparks P.** The Theory of Planned Behavior and Health Behaviors. In: Connor M, Norman P, eds. *Predicting Health Behavior*. Philadelphia: Open University Press; 1995:121-162.

96. **Boer H, Seydel ER.** Protection Motivation Theory. In: Connor M, Norman P, eds. *Predicting Health Behavior*. Philadelphia: Open University Press; 1995:94-120.
97. **Milne S, Sheeran P, Orbell S.** Prediction and intervention in health-related behavior: a meta-analytic review of protection motivation theory. *Journal of Applied Social Psychology*. 2000;30(1):106-143.
98. **Becker MH, Maiman LA, Kirscht JP, Haefner DP, Drachman RH.** The Health Belief Model and prediction of dietary compliance: a field experiment. *J Health Soc Behav*. 1977;18(4):348-66.
99. **King JB.** The impact of patients perceptions of high blood pressure on attendance at screening, An extension of the Health Belief Model. *Soc Sci Med*. 1982;16(10):1079-91.
100. **Aalto AM, Uutela A.** Glycemic control, self-care behaviors, and psychosocial factors among insulin treated diabetics: a test of an extended health belief model. *Int J Behav Med*. 1997;4(3):191-214.
101. **Gillibrand R, Stevenson J.** The extended health belief model applied to the experience of diabetes in young people. *Br J Health Psychol*. 2006;11(Pt 1):155-69.
102. **Brown CM, Segal R.** The effects of health and treatment perceptions on the use of prescribed medication and home remedies among African American and white American hypertensives. *Soc Sci Med*. 1996;43(6):903-17.
103. **Reid LD, Christensen DB.** A Psychosocial perspective in the explanation of patients' drug-taking behavior. *Social Science and Medicine*. 1988;27(3):277-285.
104. **Ali NS.** Predictors of Osteoporosis Prevention Among College Women. *American Journal of Health Behavior*. 1996;20(6):379-388.
105. **Blalock SJ, DeVellis RF, Giorgino KB, et al.** Osteoporosis prevention in premenopausal women: using a stage model approach to examine the predictors of behavior. *Health Psychol*. 1996;15(2):84-93.
106. **Chang SF, Chen CM, Chen PL, Chung UL.** Predictors of community women's osteoporosis prevention intention--a pilot study. *J Nurs Res*. 2003;11(4):231-40.
107. **Tussing L, Chapman-Novakofski K.** Osteoporosis prevention education: behavior theories and calcium intake. *J Am Diet Assoc*. 2005;105(1):92-7.
108. **Wallace LS.** Osteoporosis prevention in college women: application of the expanded health belief model. *Am J Health Behav*. 2002;26(3):163-72.
109. **Engels Y, van Assema P, Dorant E, Lechner L.** Factors associated with the intention to use vitamin D supplements: quantitative study among a sample of elderly people in a medium-sized town in the Netherlands. *J Nutr Educ*. 2001;33(3):134-42.
110. **Pressman A, Forsyth B, Ettinger B, Tosteson AN.** Initiation of osteoporosis treatment after bone mineral density testing. *Osteoporos Int*. 2001;12(5):337-42.
111. **Rubin SM, Cummings SR.** Results of bone densitometry affect women's decisions about taking measures to prevent fractures. *Ann Intern Med*. 1992;116(12 Pt 1):990-5.

112. **Rimes KA, Salkovskis PM, Shipman AJ.** Psychological and Behavioral Effects of Bone Density Screening for Osteoporosis. *Psychology & Health*. 1999;14:585-608.
113. **Solomon DH, Levin E, Helfgott SM.** Patterns of medication use before and after bone densitometry: factors associated with appropriate treatment. *J Rheumatol*. 2000;27(6):1496-500.
114. **Weinstein N.** The Precaution Adoption Process. *Health Psychology*. 1988;7(4):355-386.
115. **Weinstein N, Lyon J, Sandman P, Cuite C.** Experimental evidence for stages of health behavior change: the Precaution Adoption Process Model applied to home radon testing. *Health Psychology*. 1998;17(5):445-453.
116. **Werner P.** Knowledge about osteoporosis: assessment, correlates and outcomes. *Osteoporos Int*. 2005;16(2):115-127.
117. **Ailinger RL, Braun MA, Lasus H, Whitt K.** Factors influencing osteoporosis knowledge: a community study. *J Community Health Nurs*. 2005;22(3):135-42.
118. **Anderson KD, Chad KE, Spink KS.** Osteoporosis knowledge, beliefs, and practices among adolescent females. *J Adolesc Health*. 2005;36(4):305-12.
119. **Blalock SJ, Norton LL, Patel RA, Dooley MA.** Patient knowledge, beliefs, and behavior concerning the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum*. 2005;53(5):732-9.
120. **Drozdzowska B, Pluskiewicz W, Skiba M.** Knowledge about osteoporosis in a cohort of Polish females: the influence of age, level of education and personal experiences. *Osteoporos Int*. 2004;15(8):645-8.
121. **Juby AG, Davis P.** A prospective evaluation of the awareness, knowledge, risk factors and current treatment of osteoporosis in a cohort of elderly subjects. *Osteoporos Int*. 2001;12(8):617-22.
122. **Kulp JL, Rane S, Bachmann G.** Impact of preventive osteoporosis education on patient behavior: immediate and 3-month follow-up. *Menopause*. 2004;11(1):116-9.
123. **Kutsal YG, Atalay A, Arslan S, et al.** Awareness of osteoporotic patients. *Osteoporos Int*. 2005;16(2):128-33.
124. **Larkey LK, Day SH, Houtkooper L, Renger R.** Osteoporosis prevention: knowledge and behavior in a southwestern community. *J Community Health*. 2003;28(5):377-88.
125. **Satterfield T, Johnson SM, Slovic P, Neil N, Schein JR.** Perceived risks and reported behaviors associated with osteoporosis and its treatment. *Women Health*. 2000;31(4):21-40.
126. **Werner P, Olchovsky D, Shemi G, Vered I.** Osteoporosis health-related behaviors in secular and orthodox Israeli Jewish women. *Maturitas*. 2003;46(4):283-94.
127. **Werner P.** Knowledge and correlates of osteoporosis: a comparison of Israeli-Jewish and Israeli-Arab women. *J Women Aging*. 2003;15(4):33-49.
128. **Babbar RK, Handa AB, Lo CM, et al.** Bone health of immigrant Chinese women living in New York City. *J Community Health*. 2006;31(1):7-23.

129. **Burgener M, Arnold M, Katz JN, et al.** Older adults' knowledge and beliefs about osteoporosis: results of semistructured interviews used for the development of educational materials. *J Rheumatol*. 2005;32(4):673-7.
130. **Edwards BJ, Iris M, Ferkel E, Feinglass J.** Postmenopausal women with minimal trauma fractures are unapprised of the existence of low bone mass or osteoporosis. *Maturitas*. 2006;53(3):260-6.
131. **Ungan M, Tumer M.** Turkish women's knowledge of osteoporosis. *Fam Pract*. 2001;18(2):199-203.
132. **Pande K, Pande S, Tripathi S, Kanoi R, Thakur A, Patle S.** Poor knowledge about osteoporosis in learned Indian women. *J Assoc Physicians India*. 2005;53:433-6.
133. **Solomon DH, Finkelstein JS, Polinski JM, et al.** A randomized controlled trial of mailed osteoporosis education to older adults. *Osteoporos Int*. 2006;17(5):760-7.
134. **Winzenberg TM, Oldenburg B, Frendin S, Jones G.** The design of a valid and reliable questionnaire to measure osteoporosis knowledge in women: the Osteoporosis Knowledge Assessment Tool (OKAT). *BMC Musculoskelet Disord*. 2003;4:17.
135. **Unson C, Siccion E, Gaztambide J, Gaztambide S, Trella P, Prestwood K.** Noncompliance and osteoporosis treatment preferences of older women: a qualitative study. *Journal of Women's Health*. 2003;12(10):1037-1045.
136. **Britten N.** Patients' ideas about medicines: a qualitative study in a general practice population. *Br J Gen Pract*. 1994;44(387):465-8.
137. **Conrad P.** The Meaning of Medications: another look at compliance. *Social Science and Medicine*. 1985;20(1):29-37.
138. **Adams S, Pill R, Jones A.** Medication, chronic illness, and identity: the perspective of people with asthma. *Social Science and Medicine*. 1997;45(2):189-201.
139. **Jette AM, Cummings KM, Brock BM, Phelps MC, Naessens J.** The structure and reliability of health belief indices. *Health Serv Res*. 1981;16(1):81-98.
140. **Lin EH, Von Korff M, Ludman EJ, et al.** Enhancing compliance to prevent depression relapse in primary care. *Gen Hosp Psychiatry*. 2003;25(5):303-10.
141. **McDonald-Miszczak L, Maris P, Fitzgibbon T, Ritchie G.** A pilot study examining older adults' beliefs related to medication compliance: the BERMA survey. *J Aging Health*. 2004;16(5):591-614.
142. **Horne R, Weinman J, Hankins M.** The Beliefs about Medicines Questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health*. 1999;14:1-24.
143. **Horne R, Weinman J.** Patients' beliefs about prescribed medicines and their role in compliance to treatment in chronic physical illness. *J Psychosom Res*. 1999;47(6):555-67.
144. **Byer B, Myers LB.** Psychological correlates of compliance to medication in asthma. *Psychol Health Med*. 2000;5(4):389-393.

145. **Horne R, Weinman J.** Self-regulation and self-management in asthma: exploring the role of illness perception and treatment beliefs in explaining non-compliance to preventer medication. *Psychol Health*. 2002;17:17-32.
146. **Horne R, Buick D, Fisher M, Leake H, Cooper V, Weinman J.** Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-compliance to HAART. *Int J STD AIDS*. 2004;15(1):38-44.
147. **Horne R, Cooper V, Gellaitry G, Date HL, Fisher M.** Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and compliance: the utility of the necessity-concerns framework. *J Acquir Immune Defic Syndr*. 2007;45(3):334-41.
148. **Adams AS, Soumerai SB, Ross-Degnan D.** Use of antihypertensive drugs by Medicare enrollees: does type of drug coverage matter? *Health Aff (Millwood)*. 2001;20(1):276-86.
149. **Blustein J.** Drug coverage and drug purchases by Medicare beneficiaries with hypertension. *Health Aff (Millwood)*. 2000;19(2):219-30.
150. **Babazono A, Miyazaki M, Imatoh T, et al.** Effects of the increase in co-payments from 20 to 30 percent on the compliance rate of patients with hypertension or diabetes mellitus in the employed health insurance system. *Int J Technol Assess Health Care*. 2005;21(2):228-33.
151. **Christian-Herman J, Emons M, George D.** Effects of generic-only drug coverage in a Medicare HMO. *Health Aff (Millwood)*. 2004;Suppl Web Exclusives:W4-455-68.
152. **Federman AD, Adams AS, Ross-Degnan D, Soumerai SB, Ayanian JZ.** Supplemental insurance and use of effective cardiovascular drugs among elderly medicare beneficiaries with coronary heart disease. *Jama*. 2001;286(14):1732-9.
153. **Blais L, Couture J, Rahme E, LeLorier J.** Impact of a cost sharing drug insurance plan on drug utilization among individuals receiving social assistance. *Health Policy*. 2003;64(2):163-72.
154. **Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM.** Suboptimal statin compliance and discontinuation in primary and secondary prevention populations. *J Gen Intern Med*. 2004;19(6):638-45.
155. **Pilote L, Beck C, Richard H, Eisenberg MJ.** The effects of cost-sharing on essential drug prescriptions, utilization of medical care and outcomes after acute myocardial infarction in elderly patients. *Cmaj*. 2002;167(3):246-52.
156. **Soumerai SB, Avorn J, Ross-Degnan D, Gortmaker S.** Payment restrictions for prescription drugs under Medicaid. Effects on therapy, cost, and equity. *N Engl J Med*. 1987;317(9):550-6.
157. **Soumerai SB, McLaughlin TJ, Ross-Degnan D, Casteris CS, Bollini P.** Effects of a limit on Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. *N Engl J Med*. 1994;331(10):650-5.
158. **Dor A, Encinosa W.** (National Bureau of Economic Research). Does Cost Sharing Affect Compliance?
The Case of Prescription Drugs. 2004 NBER Working Paper No. 10738.

159. **Goldman DP, Joyce GF, Escarce JJ, et al.** Pharmacy benefits and the use of drugs by the chronically ill. *Jama*. 2004;291(19):2344-50.
160. **Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Frank RG.** The effect of incentive-based formularies on prescription-drug utilization and spending. *N Engl J Med*. 2003;349(23):2224-32.
161. **Huskamp HA, Deverka PA, Epstein AM, et al.** Impact of 3-tier formularies on drug treatment of attention-deficit/hyperactivity disorder in children. *Arch Gen Psychiatry*. 2005;62(4):435-41.
162. **Ozminkowski RJ, Marder WD, Hawkins K, et al.** The use of disease-modifying new drugs for multiple sclerosis treatment in private-sector health plans. *Clin Ther*. 2004;26(8):1341-54.
163. **Roblin DW, Platt R, Goodman MJ, et al.** Effect of increased cost-sharing on oral hypoglycemic use in five managed care organizations: how much is too much? *Med Care*. 2005;43(10):951-9.
164. **Tamblyn R, Laprise R, Hanley JA, et al.** Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *Jama*. 2001;285(4):421-9.
165. **Klein D, Turvey C, Wallace R.** Elders who delay medication because of cost: health insurance, demographic, health, and financial correlates. *Gerontologist*. 2004;44(6):779-87.
166. **Heisler M, Langa KM, Eby EL, Fendrick AM, Kabeto MU, Piette JD.** The health effects of restricting prescription medication use because of cost. *Med Care*. 2004;42(7):626-34.
167. **Heisler M, Wagner TH, Piette JD.** Patient strategies to cope with high prescription medication costs: who is cutting back on necessities, increasing debt, or underusing medications? *J Behav Med*. 2005;28(1):43-51.
168. **Piette JD, Heisler M, Wagner TH.** Problems paying out-of-pocket medication costs among older adults with diabetes. *Diabetes Care*. 2004;27(2):384-91.
169. **Piette JD, Heisler M, Wagner TH.** Cost-related medication underuse among chronically ill adults: the treatments people forgo, how often, and who is at risk. *Am J Public Health*. 2004;94(10):1782-7.
170. **Piette JD, Wagner TH, Potter MB, Schillinger D.** Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. *Med Care*. 2004;42(2):102-9.
171. **Sharkey JR, Ory MG, Browne BA.** Determinants of self-management strategies to reduce out-of-pocket prescription medication expense in homebound older people. *J Am Geriatr Soc*. 2005;53(4):666-74.
172. **Steinman MA, Sands LP, Covinsky KE.** Self-restriction of medications due to cost in seniors without prescription coverage. *J Gen Intern Med*. 2001;16(12):793-9.
173. **Stuart B, Grana J.** Ability to pay and the decision to medicate. *Med Care*. 1998;36(2):202-11.
174. **Chisholm MA, Vollenweider LJ, Mulloy LL, et al.** Renal transplant patient compliance with free immunosuppressive medications. *Transplantation*. 2000;70(8):1240-4.

175. **Mahoney JJ.** Reducing patient drug acquisition costs can lower diabetes health claims. *Am J Manag Care*. 2005;11(5 Suppl):S170-6.
176. **Schoen MD, DiDomenico RJ, Connor SE, Dischler JE, Bauman JL.** Impact of the cost of prescription drugs on clinical outcomes in indigent patients with heart disease. *Pharmacotherapy*. 2001;21(12):1455-63.
177. **Soumerai SB, Ross-Degnan D, Avorn J, McLaughlin T, Choodnovskiy I.** Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes. *N Engl J Med*. 1991;325(15):1072-7.
178. **Col N, Fanale JE, Kronholm P.** The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med*. 1990;150(4):841-5.
179. **Schafheutle EI, Hassell K, Noyce PR, Weiss MC.** Access to medicines: cost as an influence on the views and behaviour of patients. *Health Soc Care Community*. 2002;10(3):187-95.
180. **Piette JD, Heisler M, Krein S, Kerr EA.** The role of patient-physician trust in moderating medication noncompliance due to cost pressures. *Arch Intern Med*. 2005;165(15):1749-55.
181. **Claxton AJ, Cramer J, Pierce C.** A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-310.
182. **Cramer J, Vachon L, Desforges C, Sussman NM.** Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. *Epilepsia*. 1995;36(11):1111-7.
183. **Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR.** The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med*. 1990;150(9):1881-4.
184. **Greenberg RN.** Overview of patient compliance with medication dosing: a literature review. *Clin Ther*. 1984;6(5):592-9.
185. **Paes AH, Bakker A, Soe-Agnie CJ.** Impact of dosage frequency on patient compliance. *Diabetes Care*. 1997;20(10):1512-7.
186. **Ammassari A, Trotta MP, Murri R, et al.** Correlates and predictors of compliance to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr*. 2002;31 Suppl 3:S123-7.
187. **Stone VE, Hogan JW, Schuman P, et al.** Antiretroviral regimen complexity, self-reported compliance, and HIV patients' understanding of their regimens: survey of women in the her study. *J Acquir Immune Defic Syndr*. 2001;28(2):124-31.
188. **Kogut SJ, Andrade SE, Willey C, Larrat EP.** Noncompliance as a predictor of antidiabetic drug therapy intensification (augmentation). *Pharmacoepidemiol Drug Saf*. 2004;13(9):591-8.
189. **Venturini F, Nichol MB, Sung JC, Bailey KL, Cody M, McCombs JS.** Compliance with sulfonylureas in a health maintenance organization: a pharmacy record-based study. *Ann Pharmacother*. 1999;33(3):281-8.
190. **Grant RW, Devita NG, Singer DE, Meigs JB.** Polypharmacy and medication compliance in patients with type 2 diabetes. *Diabetes Care*. 2003;26(5):1408-12.

191. **Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E.** Compliance to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clin Ther*. 2002;24(3):460-7.
192. **Paterson DL, Swindells S, Mohr J, et al.** Compliance to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133(1):21-30.
193. **Pyon EY.** Once-monthly ibandronate for postmenopausal osteoporosis: review of a new dosing regimen. *Clin Ther*. 2006;28(4):475-90.
194. **Berkman LF, Glass T.** Social Integration, Social Networks, Social Support, and Health. In: Berkman LF, Kawachi I, eds. *Social Epidemiology*. New York: Oxford University Press; 2000:137-173.
195. **House JS, Landis KR, Umberson D.** Social relationships and health. *Science*. 1988;241(4865):540-5.
196. **DiMatteo MR.** Social support and patient compliance to medical treatment: a meta-analysis. *Health Psychol*. 2004;23(2):207-18.
197. **Belgrave FZ, Lewis DM.** The role of social support in compliance and other health behaviors for African Americans with chronic illnesses. *J Health Soc Policy*. 1994;5(3-4):55-68.
198. **Kidd KE, Altman DG.** Compliance in social context. *Control Clin Trials*. 2000;21(5 Suppl):184S-7S.
199. **Anderson RT, Ory M, Cohen S, McBride JS.** Issues of aging and compliance to health interventions. *Control Clin Trials*. 2000;21(5 Suppl):171S-83S.
200. **Dobbels F, Vanhaecke J, Desmyttere A, Dupont L, Nevens F, De Geest S.** Prevalence and correlates of self-reported pretransplant noncompliance with medication in heart, liver, and lung transplant candidates. *Transplantation*. 2005;79(11):1588-95.
201. **Doherty WJ, Schrott HG, Metcalf L, Iasiello-Vailas L.** Effect of spouse support and health beliefs on medication compliance. *J Fam Pract*. 1983;17(5):837-41.
202. **Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz J.** Sociodemographic and psychological variables influencing compliance to antiretroviral therapy. *Aids*. 1999;13(13):1763-9.
203. **Hershey JC, Morton BG, Davis JB, Reichgott MJ.** Patient compliance with antihypertensive medication. *Am J Public Health*. 1980;70(10):1081-9.
204. **Irvine J, Baker B, Smith J, et al.** Poor compliance to placebo or amiodarone therapy predicts mortality: results from the CAMIAT study. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial. *Psychosom Med*. 1999;61(4):566-75.
205. **Kalichman SC, Ramachandran B, Catz S.** Compliance to combination antiretroviral therapies in HIV patients of low health literacy. *J Gen Intern Med*. 1999;14(5):267-73.
206. **Schwarzer R, Fuchs R.** Self-efficacy and health behaviors. In: Connor M, Norman P, eds. *Predicting Health Behavior*. Philadelphia: Open University Press; 1995:163-196.

207. **Senecal C, Nouwen A, White D.** Motivation and dietary self-care in adults with diabetes: are self-efficacy and autonomous self-regulation complementary or competing constructs? *Health Psychol*. 2000;19(5):452-7.
208. **Van Der Ven NC, Weinger K, Yi J, et al.** The confidence in diabetes self-care scale: psychometric properties of a new measure of diabetes-specific self-efficacy in Dutch and US patients with type 1 diabetes. *Diabetes Care*. 2003;26(3):713-8.
209. **Resnick B, Wehren L, Orwig D.** Reliability and validity of the self-efficacy and outcome expectations for osteoporosis medication compliance scales. *Orthop Nurs*. 2003;22(2):139-47.
210. **Gould ON, McDonald-Miszcak L, King B.** Metacognition and medication compliance: how do older adults remember? *Experimental Aging Research*. 1997;23:315-342.
211. **Wroe AL.** Intentional and unintentional noncompliance: a study of decision making. *J Behav Med*. 2002;25(4):355-72.
212. **Gray SL, Mahoney JE, Blough DK.** Medication compliance in elderly patients receiving home health services following hospital discharge. *Ann Pharmacother*. 2001;35(5):539-45.
213. **Salas M, In't Veld BA, van der Linden PD, Hofman A, Breteler M, Stricker BH.** Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. *Clin Pharmacol Ther*. 2001;70(6):561-6.
214. **Rosen MI, Beauvais JE, Rigsby MO, Salahi JT, Ryan CE, Cramer JA.** Neuropsychological correlates of suboptimal compliance to metformin. *J Behav Med*. 2003;26(4):349-60.
215. **Kiortsis DN, Giral P, Bruckert E, Turpin G.** Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *J Clin Pharm Ther*. 2000;25(6):445-51.
216. **Iskedjian M, Einarson TR, MacKeigan LD, et al.** Relationship between daily dose frequency and compliance to antihypertensive pharmacotherapy: evidence from a meta-analysis. *Clin Ther*. 2002;24(2):302-16.
217. **Graveley E, Oseasohn C.** Multiple drug regimens: medication compliance among Veterans 65 years and older. *Research in Nursing and Health*. 1991;14:51-58.
218. **Donnan PT, MacDonald TM, Morris AD.** Compliance to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med*. 2002;19(4):279-84.
219. **Nutting PA, Rost K, Smith J, Werner JJ, Elliot C.** Competing demands from physical problems: effect on initiating and completing depression care over 6 months. *Arch Fam Med*. 2000;9(10):1059-64.
220. **McLane CG, Zyzanski SJ, Flocke SA.** Factors associated with medication noncompliance in rural elderly hypertensive patients. *Am J Hypertens*. 1995;8(2):206-9.
221. **McElnay JC, McCallion CR, al-Deagi F, Scott M.** Self-reported medication non-compliance in the elderly. *Eur J Clin Pharmacol*. 1997;53(3-4):171-8.

222. **Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA.** Predictors of medication noncompliance in a sample of older adults. *Clin Ther*. 1994;16(1):110-7.
223. **Hulka BS, Cassel JC, Kupper LL, Burdette JA.** Communication, compliance, and concordance between physicians and patients with prescribed medications. *Am J Public Health*. 1976;66(9):847-53.
224. **Ciechanowski PS, Katon WJ, Russo JE.** Depression and diabetes: impact of depressive symptoms on compliance, function, and costs. *Arch Intern Med*. 2000;160(21):3278-85.
225. **Kilbourne AM, Reynolds CF, 3rd, Good CB, Sereika SM, Justice AC, Fine MJ.** How does depression influence diabetes medication compliance in older patients? *Am J Geriatr Psychiatry*. 2005;13(3):202-10.
226. **Lerman I, Lozano L, Villa AR, et al.** Psychosocial factors associated with poor diabetes self-care management in a specialized center in Mexico City. *Biomed Pharmacother*. 2004;58(10):566-70.
227. **Lin EH, Katon W, Von Korff M, et al.** Relationship of depression and diabetes self-care, medication compliance, and preventive care. *Diabetes Care*. 2004;27(9):2154-60.
228. **Park H, Hong Y, Lee H, Ha E, Sung Y.** Individuals with type 2 diabetes and depressive symptoms exhibited lower compliance with self-care. *J Clin Epidemiol*. 2004;57(9):978-84.
229. **van Servellen G, Chang B, Garcia L, Lombardi E.** Individual and system level factors associated with treatment noncompliance in human immunodeficiency virus-infected men and women. *AIDS Patient Care STDS*. 2002;16(6):269-81.
230. **Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J.** Psychological and cognitive function: predictors of compliance with cholesterol lowering treatment. *Ann Behav Med*. 2004;27(2):117-24.
231. **Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Avorn J.** Noncompliance with congestive heart failure therapy in the elderly. *Arch Intern Med*. 1994;154(4):433-7.
232. **Vik SA, Maxwell CJ, Hogan DB.** Measurement, correlates, and health outcomes of medication compliance among seniors. *Ann Pharmacother*. 2004;38(2):303-12.
233. **Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J.** The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. *Am J Hypertens*. 1997;10(7 Pt 1):697-704.
234. **Ellis J.** Prospective memory and medicine taking. In: Myers LB, Midence K, eds. *Compliance to Treatment in Medical Conditions*. Amsterdam: Harwood Academic Publishers; 1998:113-131.
235. **Tones K.** Health promotion: empowering choice. In: Myers L, Midence K, eds. *Compliance to treatment in medical conditions*. Amsterdam: Harwood Academic Publishers; 1998:133-160.

236. **Meyer D, Leventhal H, Gutmann M.** Common-sense models of illness: the example of hypertension. *Health Psychology*. 1985;4(2):115-135.
237. **Clifford S, Barber N, Horne R.** Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: Application of the Necessity-Concerns Framework. *J Psychosom Res*. 2008;64:41-46.
238. **Svarstad BL, Chewning BA, Sleath BL, Claesson C.** The Brief Medication Questionnaire: a tool for screening patient compliance and barriers to compliance. *Patient Educ Couns*. 1999;37(2):113-24.
239. **Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J.** Can simple clinical measurements detect patient noncompliance? *Hypertension*. 1980;2(6):757-64.
240. **Kimmerling M, Wagner G, Ghosh-Dastidar B.** Factors associated with accurate self-reported compliance to HIV antiretrovirals. *Int J STD AIDS*. 2003;14(4):281-4.
241. **Farmer KC.** Methods for measuring and monitoring medication regimen compliance in clinical trials and clinical practice. *Clin Ther*. 1999;21(6):1074-90; discussion 1073.
242. **Wandless I, Mucklow JC, Smith A, Prudham D.** Compliance with prescribed medicines: a study of elderly patients in the community. *J R Coll Gen Pract*. 1979;29(204):391-6.
243. **Butler JA, Peveler RC, Roderick P, Smith PW, Horne R, Mason JC.** Modifiable risk factors for non-compliance to immunosuppressants in renal transplant recipients: a cross-sectional study. *Nephrol Dial Transplant*. 2004;19(12):3144-9.
244. **Holzemer WL, Bakken S, Portillo CJ, et al.** Testing a nurse-tailored HIV medication compliance intervention. *Nurs Res*. 2006;55(3):189-97.
245. **Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB.** The concordance of self-report with other measures of medication compliance: a summary of the literature. *Med Care*. 2004;42(7):649-52.
246. **Wang PS, Benner JS, Glynn RJ, Winkelmayer WC, Mogun H, Avorn J.** How well do patients report noncompliance with antihypertensive medications?: a comparison of self-report versus filled prescriptions. *Pharmacoepidemiol Drug Saf*. 2004;13(1):11-9.
247. **Choo PW, Rand CS, Inui TS, et al.** Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of compliance to antihypertensive therapy. *Med Care*. 1999;37(9):846-57.
248. **Blumberg EJ, Hovell MF, Kelley NJ, Vera AY, Sipan CL, Berg JP.** Self-report INH compliance measures were reliable and valid in Latino adolescents with latent tuberculosis infection. *J Clin Epidemiol*. 2005;58(6):645-8.
249. **Steiner JF, Prochazka AV.** The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50(1):105-16.
250. **Lau HS, de Boer A, Beuning KS, Porsius A.** Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol*. 1997;50(5):619-25.

251. **Freburger JK, Callahan LF, Currey SS, Anderson LA.** Use of the Trust in Physician Scale in patients with rheumatic disease: psychometric properties and correlates of trust in the rheumatologist. *Arthritis Rheum*. 2003;49(1):51-8.
252. **O'Leary A.** Self-efficacy and health. *Behav Res Ther*. 1985;23(4):437-51.
253. **Strecher VJ, DeVellis BM, Becker MH, Rosenstock IM.** The role of self-efficacy in achieving health behavior change. *Health Educ Q*. 1986;13(1):73-92.
254. **Usherwood T, Jones N.** Self-perceived health status of hostel residents: use of the SF-36D health survey questionnaire. Hanover Project Team. *J Public Health Med*. 1993;15(4):311-4.
255. **Lacroix AZ, Buist DS, Brenneman SK, Abbott TA, 3rd.** Evaluation of three population-based strategies for fracture prevention: results of the osteoporosis population-based risk assessment (OPRA) trial. *Med Care*. 2005;43(3):293-302.
256. **Gerend MA, Aiken LS, West SG, Erchull MJ.** Beyond medical risk: investigating the psychological factors underlying women's perceptions of susceptibility to breast cancer, heart disease, and osteoporosis. *Health Psychol*. 2004;23(3):247-58.
257. **Gerend MA, Aiken LS, West SG.** Personality factors in older women's perceived susceptibility to diseases of aging. *J Pers*. 2004;72(2):243-70.
258. **Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A.** Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465-75.
259. **Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV.** Residual lifetime risk of fractures in women and men. *J Bone Miner Res*. 2007;22(6):781-8.
260. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*. 1996;348(9041):1535-41.
261. **Harris ST, Watts NB, Genant HK, et al.** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999;282(14):1344-52.
262. **Reginster J, Minne HW, Sorensen OH, et al.** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int*. 2000;11(1):83-91.
263. **Wells G, Cranney A, Peterson J, et al.** Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008(1):CD004523.
264. **MacLean C, Newberry S, Maglione M, et al.** Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med*. 2008;148(3):197-213.
265. **Carr AJ, Thompson PW, Cooper C.** Factors associated with compliance and persistence to bisphosphonate therapy in osteoporosis: a cross-sectional survey. *Osteoporos Int*. 2006;17(11):1638-44.

266. **Horne R, Weinman J, Hankins M.** The Beliefs about Medications Questionnaire: the development of a new method for assessing the cognitive representation about medication. *Psychol Health*. 1999;14:1-24.
267. **Horne R.** Patients' beliefs about treatment: the hidden determinant of treatment outcome? *J Psychosom Res*. 1999;47(6):491-5.
268. **Wroe AL, Thomas MG.** Intentional and unintentional non-compliance in patients prescribed HAART treatment regimens. *Psychol Health Med*. 2003;8:453-463.
269. **Newey WK.** Efficient estimation of limited dependent variable models with endogenous explanatory variables. *Journal of Econometrics*. 1987;36:231-250.
270. **Brown C, Battista DR, Bruehlman R, Sereika SS, Thase ME, Dunbar-Jacob J.** Beliefs about antidepressant medications in primary care patients: relationship to self-reported compliance. *Med Care*. 2005;43(12):1203-7.
271. **Kamatari M, Koto S, Ozawa N, et al.** Factors affecting long-term compliance of osteoporotic patients with bisphosphonate treatment and QOL assessment in actual practice: alendronate and risedronate. *J Bone Miner Metab*. 2007;25(5):302-9.
272. **Unson CG, Siccion E, Gaztambide J, Gaztambide S, Mahoney Trella P, Prestwood K.** Noncompliance and osteoporosis treatment preferences of older women: a qualitative study. *J Womens Health (Larchmt)*. 2003;12(10):1037-45.
273. **Sinsky CA, Foreman-Hoffman V, Cram P.** The impact of expressions of treatment efficacy and out-of-pocket expenses on patient and physician interest in osteoporosis treatment: implications for pay-for-performance programs. *J Gen Intern Med*. 2008;23(2):164-8.
274. **Lloyd A, McIntosh E, Price M.** The importance of drug adverse effects compared with seizure control for people with epilepsy: a discrete choice experiment. *Pharmacoeconomics*. 2005;23(11):1167-81.
275. **Lau E, Papaioannou A, Dolovich L, et al.** Patients' compliance to osteoporosis therapy: exploring the perceptions of postmenopausal women. *Can Fam Physician*. 2008;54(3):394-402.
276. **Lancsar EJ, Hall JP, King M, et al.** Using discrete choice experiments to investigate subject preferences for preventive asthma medication. *Respirology*. 2007;12(1):127-36.
277. **Keen R, Jodar E, Iolascon G, et al.** European women's preference for osteoporosis treatment: influence of clinical effectiveness and dosing frequency. *Curr Med Res Opin*. 2006;22(12):2375-81.
278. **Fraenkel L, Constantinescu F, Oberto-Medina M, Wittink DR.** Women's preferences for prevention of bone loss. *J Rheumatol*. 2005;32(6):1086-92.
279. **Duarte JW, Bolge SC, Sen SS.** An evaluation of patients' preferences for osteoporosis medications and their attributes: the PREFER-International study. *Clin Ther*. 2007;29(3):488-503.
280. **Benson J, Britten N.** Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *BMJ*. 2002;325(7369):873.
281. **Adams S, Pill R, Jones A.** Medication, chronic illness and identity: the perspective of people with asthma. *Soc Sci Med*. 1997;45(2):189-201.

282. **Conrad P.** The meaning of medications: another look at compliance. *Soc Sci Med*. 1985;20(1):29-37.
283. **Donovan JL, Blake DR.** Patient non-compliance: deviance or reasoned decision-making? *Soc Sci Med*. 1992;34(5):507-13.
284. **de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, Pols HA, Koes BW, Steyerberg EW.** Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. *Osteoporos Int*. 2008;19(7):1029-37.
285. **Mason BJ, Matsuyama JR, Jue SG.** Assessment of sulfonylurea compliance and metabolic control. *Diabetes Educ*. 1995;21(1):52-7.
286. **Wells GA, Cranney A, Peterson J, et al.** Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008(1):CD001155.
287. **Black DM, Schwartz AV, Ensrud KE, et al.** Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *Jama*. 2006;296(24):2927-38.
288. **Hyre AD, Krousel-Wood MA, Muntner P, Kawasaki L, DeSalvo KB.** Prevalence and predictors of poor antihypertensive medication compliance in an urban health clinic setting. *J Clin Hypertens (Greenwich)*. 2007;9(3):179-86.
289. **Taira DA, Gelber RP, Davis J, Gronley K, Chung RS, Seto TB.** Antihypertensive compliance and drug class among Asian Pacific Americans. *Ethn Health*. 2007;12(3):265-81.
290. **Bender BG, Bender SE.** Patient-identified barriers to asthma treatment compliance: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am*. 2005;25(1):107-30.
291. **Ediger JP, Walker JR, Graff L, et al.** Predictors of medication compliance in inflammatory bowel disease. *Am J Gastroenterol*. 2007;102(7):1417-26.
292. **Menckeberg TT, Bouvy ML, Bracke M, et al.** Beliefs about medicines predict refill compliance to inhaled corticosteroids. *J Psychosom Res*. 2008;64(1):47-54.
293. **Ringe JD, Christodoulakos GE, Mellstrom D, et al.** Patient compliance with alendronate, risedronate and raloxifene for the treatment of osteoporosis in postmenopausal women. *Curr Med Res Opin*. 2007;23(11):2677-87.
294. **Black DM, Arden NK, Palermo L, Pearson J, Cummings SR.** Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1999;14(5):821-8.
295. **Siris ES, Genant HK, Laster AJ, Chen P, Misurski DA, Krege JH.** Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporos Int*. 2007;18(6):761-70.
296. **Schousboe JT, Fink HA, Lui LY, Taylor BC, Ensrud KE.** Association between prior non-spine non-hip fractures or prevalent radiographic vertebral deformities known to be at least 10 years old and incident hip fracture. *J Bone Miner Res*. 2006;21(10):1557-64.
297. **Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS.** Physician communication when prescribing new medications. *Arch Intern Med*. 2006;166(17):1855-62.

298. **Beach MC, Sugarman J, Johnson RL, Arbelaez JJ, Duggan PS, Cooper LA.** Do Patients Treated With Dignity Report Higher Satisfaction, Compliance, and Receipt of Preventive Care? *Ann Fam Med*. 2005;3:331-338.
299. **Bissell P, May CR, Noyce PR.** From compliance to concordance: barriers to accomplishing a re-framed model of health care interactions. *Soc Sci Med*. 2004;58(4):851-62.
300. **Bultman DC, Svarstad BL.** Effects of physician communication style on client medication beliefs and compliance with antidepressant treatment. *Patient Educ Couns*. 2000;40(2):173-85.
301. **Stewart MA.** Effective physician-patient communication and health outcomes: a review. *CMAJ*. 1995;152(9):1423-33.
302. **Johnson MO, Chesney MA, Goldstein RB, et al.** Positive provider interactions, compliance self-efficacy, and compliance to antiretroviral medications among HIV-infected adults: A mediation model. *AIDS Patient Care STDS*. 2006;20(4):258-68.
303. **Heisler M, Cole I, Weir D, Kerr EA, Hayward RA.** Does physician communication influence older patients' diabetes self-management and glycemic control? Results from the Health and Retirement Study (HRS). *J Gerontol A Biol Sci Med Sci*. 2007;62(12):1435-42.
304. **Gonzalez J, Williams JW, Jr., Noel PH, Lee S.** Compliance to mental health treatment in a primary care clinic. *J Am Board Fam Pract*. 2005;18(2):87-96.
305. **Kerse N, Buetow S, Mainous AG, 3rd, Young G, Coster G, Arroll B.** Physician-patient relationship and medication compliance: a primary care investigation. *Ann Fam Med*. 2004;2(5):455-61.
306. **Weiss TW, McHorney CA.** Osteoporosis medication profile preference: results from the PREFER-US study. *Health Expect*. 2007;10(3):211-23.
307. **Hu L-T, Bentler PM.** Cut-off criteria for fit indices in covariance structure analysis: conventional criteria versus new alternatives. *Structural Equation Modeling*. 1999;6:1-55.
308. **Kline RB.** *Principles and Practice of Structural Equation Modeling*. 2nd ed New York: The Guilford Press; 2005.
309. **Buller M, Buller D.** Physicians' communication style and patient satisfaction. *Journal of Health and Social Behavior*. 1987;28:375-388.
310. **Ciechanowski PS, Katon WJ, Russo JE, Walker EA.** The patient-provider relationship: attachment theory and compliance to treatment in diabetes. *Am J Psychiatry*. 2001;158(1):29-35.
311. **Goff SL, Mazor KM, Meterko V, Dodd K, Sabin J.** Patients' beliefs and preferences regarding doctors' medication recommendations. *J Gen Intern Med*. 2008;23(3):236-41.
312. **Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E.** FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19(4):385-97.
313. **Fujiwara S, Nakamura T, Orimo H, et al.** Development and application of a Japanese model of the WHO fracture risk assessment tool (FRAX). *Osteoporos Int*. 2008;19(4):429-35.

314. **Kanis JA, Burlet N, Cooper C, et al.** European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2008;19(4):399-428.
315. **Dawson-Hughes B, Tosteson AN, Melton LJ, 3rd, et al.** Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int*. 2008;19(4):449-58.
316. **Hoffman C, Rice D, Sung HY.** Persons with chronic conditions. Their prevalence and costs. *JAMA*. 1996;276(18):1473-9.
317. **Epping-Jordan J, Bengoa R, Kawar R, Sabate E.** The challenge of chronic conditions: WHO responds. *BMJ*. 2001;323(7319):947-8.
318. **Wolff JL, Boult C.** Moving beyond round pegs and square holes: restructuring Medicare to improve chronic care. *Ann Intern Med*. 2005;143(6):439-45.
319. **Haynes RB, Montague P, Oliver T, McKibbon KA, Brouwers MC, Kanani R.** Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev*. 2000(2):CD000011.
320. **Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM.** The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract*. 2008;62(1):76-87.
321. **Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS.** Impact of medication compliance on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521-30.
322. **Adachi J, Lynch N, Middelhoven H, Hunjan M, Cowell W.** The association between compliance and persistence with bisphosphonate therapy and fracture risk: a review. *BMC Musculoskelet Disord*. 2007;8:97.
323. **Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd.** Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. *J Bone Miner Res*. 1992;7(2):221-7.
324. **Fink HA, Milavetz DL, Palermo L, et al.** What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? *J Bone Miner Res*. 2005;20(7):1216-22.
325. **Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M.** Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721-39.
326. **Melton LJ, 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL.** Vertebral fractures predict subsequent fractures. *Osteoporos Int*. 1999;10(3):214-21.
327. **Ross PD, Davis JW, Epstein RS, Wasnich RD.** Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med*. 1991;114(11):919-23.
328. **Melton LJ, 3rd, Lane AW, Cooper C, Eastell R, O'Fallon WM, Riggs BL.** Prevalence and incidence of vertebral deformities. *Osteoporos Int*. 1993;3(3):113-9.
329. **O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ.** The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study. *J Bone Miner Res*. 1996;11(7):1010-8.

330. **Schedlbauer A, Schroeder K, Peters TJ, Fahey T.** Interventions to improve compliance to lipid lowering medication. *Cochrane Database Syst Rev*. 2004(4):CD004371.
331. **Schroeder K, Fahey T, Ebrahim S.** How can we improve compliance to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. *Arch Intern Med*. 2004;164(7):722-32.
332. **Williams A, Manias E, Walker R.** Interventions to improve medication compliance in people with multiple chronic conditions: a systematic review. *J Adv Nurs*. 2008;63(2):132-43.
333. **Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X.** Interventions for enhancing medication compliance. *Cochrane Database Syst Rev*. 2008(2):CD000011.
334. **Bodenheimer T, Wagner EH, Grumbach K.** Improving primary care for patients with chronic illness: the chronic care model, Part 2. *JAMA*. 2002;288(15):1909-14.
335. **Theunissen NC, de Ridder DT, Bensing JM, Rutten GE.** Manipulation of patient-provider interaction: discussing illness representations or action plans concerning compliance. *Patient Educ Couns*. 2003;51(3):247-58.
336. **Berenson RA, Hammons T, Gans DN, et al.** A house is not a home: keeping patients at the center of practice redesign. *Health Aff (Millwood)*. 2008;27(5):1219-30.
337. **Wagner EH, Austin BT, Von Korff M.** Organizing care for patients with chronic illness. *Milbank Q*. 1996;74(4):511-44.
338. **Wagner EH.** Meeting the needs of chronically ill people. *BMJ*. 2001;323(7319):945-6.
339. **Wagner EH.** Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract*. 1998;1(1):2-4.
340. **Boyd CM, Boult C, Shadmi E, et al.** Guided care for multimorbid older adults. *Gerontologist*. 2007;47(5):697-704.
341. **Boult C, Reider L, Frey K, et al.** Early effects of "Guided Care" on the quality of health care for multimorbid older persons: a cluster-randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2008;63(3):321-7.
342. **Nagy VT, Wolfe GR.** Cognitive predictors of compliance in chronic disease patients. *Med Care*. 1984;22(10):912-21.
343. **Fuchs VR.** Time preference and health: an exploratory study. In: Fuchs VR, ed. *Economic Aspects of Health*. Chicago: University of Chicago Press; 1982:93-120.
344. **Roelofsma PH, van der Pligt J.** On the psychology of time preference and human decisions: introduction to the special issue. *Acta Psychol (Amst)*. 2001;108(2):91-3.
345. **Ganiats TG, Carson RT, Hamm RM, et al.** Population-based time preferences for future health outcomes. *Med Decis Making*. 2000;20(3):263-70.
346. **Hojgard S, Enemark U, Lyttkens CH, Lindgren A, Troeng T, Weibull H.** Discounting and clinical decision making: physicians, patients, the general

public, and the management of asymptomatic abdominal aortic aneurysms. *Health Econ*. 2002;11(4):355-70.

347. **Asenso-Boadi F, Peters TJ, Coast J.** Exploring differences in empirical time preference rates for health: an application of meta-regression. *Health Econ*. 2008;17(2):235-48.
348. **Sundaramurthy S, Bush TM, Neuwelt CM, Ward MM.** Time perspective predicts the progression of permanent organ damage in patients with systemic lupus erythematosus. *Lupus*. 2003;12(6):443-8.
349. **Fadiman A.** *The Spirit Catches You and You Fall Down* New York: Farrar, Strauss, and Giroux; 1997.
350. **Pachter LM.** Culture and clinical care. Folk illness beliefs and behaviors and their implications for health care delivery. *Jama*. 1994;271(9):690-4.
351. **Kaplan RC, Bhalodkar NC, Brown EJ, Jr., White J, Brown DL.** Race, ethnicity, and sociocultural characteristics predict noncompliance with lipid-lowering medications. *Prev Med*. 2004;39(6):1249-55.
352. **Horne R, Graupner L, Frost S, Weinman J, Wright SM, Hankins M.** Medicine in a multi-cultural society: the effect of cultural background on beliefs about medications. *Soc Sci Med*. 2004;59(6):1307-13.
353. **Gellad ZF, Lyles KW.** Direct-to-consumer advertising of pharmaceuticals. *Am J Med*. 2007;120(6):475-80.
354. **Vogel RJ, Ramachandran S, Zachry WM.** A 3-stage model for assessing the probable economic effects of direct-to-consumer advertising of pharmaceuticals. *Clin Ther*. 2003;25(1):309-29.

Appendix A - Survey Instrument

ABOUT YOU

1. In what year were you born?

   ☐☐☐☐

2. How many years ago were you first diagnosed with osteoporosis? (check one)

   ○ 0 to 1 year
   ○ 2 to 3 years
   ○ 4 to 6 years
   ○ 7 to 10 years
   ○ More than 10 years

3. Are you male or female? (check one)

   ○ Male
   ○ Female

4. How many different prescription medications a day do you take? (check one)

   ○ 0
   ○ 1 to 2
   ○ 3 to 4
   ○ 5 to 6
   ○ 7 or more

5. How many times a day do you have to take at least one prescription medication? (check one)

   ○ 0
   ○ 1
   ○ 2
   ○ 3
   ○ 4

TAKING MEDICATIONS FOR OSTEOPOROSIS

1. In the past 18 months, did you personally decide to stop taking any of your prescribed medications for osteoporosis, for at least 1 month, **because of side effects from the medication**? (check one)

   ○ Yes
   ○ No
   ○ Does not apply

2. In the past 18 months, did you personally decide to stop taking any of your prescribed medications for osteoporosis, for at least 1 month, **for some other reason**? (check one)

   ○ Yes
   ○ No
   ○ Does not apply

Please go to next page

People will sometimes miss a dose of one or more of their medications for a variety of reasons. These questions ask about your use of **prescription medication for osteoporosis** (not calcium or vitamin D) over the past month.

3. Over the PAST MONTH, **how many times, if at all,** did you forget to take 1 or more of your prescribed medications for osteoporosis? (check one)

   ○ None
   ○ One time
   ○ Two times
   ○ Three or more times
   ○ I am no longer taking any medications for osteoporosis

4. Over the PAST MONTH, **how many times, if at all,** did you decide to skip 1 or more of your prescribed medications for osteoporosis to suit your needs? (check one)

   ○ None
   ○ One time
   ○ Two times
   ○ Three or more times
   ○ I am no longer taking any medications for osteoporosis

CONCERNS ABOUT MEDICATIONS

Please answer these questions even if you do not currently routinely take medication.

(check one response for each item)	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
1. I sometimes worry about becoming too dependent on medicines	○	○	○	○	○	○
2. I am concerned about the long-term effects of medicines	○	○	○	○	○	○
3. Medicines are a mystery to me	○	○	○	○	○	○
4. If doctors had more time with patients, they would prescribe fewer medicines	○	○	○	○	○	○
5. Doctors use too many medicines	○	○	○	○	○	○
6. Natural remedies are safer than medicines	○	○	○	○	○	○

Please go to next page

(check one response for each item)	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
7. Medicines should be used only as a last resort	○	○	○	○	○	○
8. Medicines do more harm than good	○	○	○	○	○	○
9. People who take medicines should stop their treatment for a while every now and then	○	○	○	○	○	○
10. Most medicines are addictive	○	○	○	○	○	○
11. It is too easy to become dependent on medicines	○	○	○	○	○	○
12. Most medicines are safe if they are taken correctly	○	○	○	○	○	○
13. Taking medication makes me feel that I am an unhealthy person	○	○	○	○	○	○
14. Taking medication makes me feel that I am a weak person	○	○	○	○	○	○
15. Taking medication makes me feel like I am not a whole person	○	○	○	○	○	○

NEED FOR MEDICATIONS FOR OSTEOPOROSIS

(check one response for each item)	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
1. My health, at present, depends on my medicine for osteoporosis	○	○	○	○	○	○
2. My health, in the future, will depend on medicine to treat osteoporosis	○	○	○	○	○	○
3. My medicine for osteoporosis protects me from getting worse	○	○	○	○	○	○

Please go to next page

(check one response for each item)	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
4. Without medicine for osteoporosis, I am very susceptible to having broken bones	○	○	○	○	○	○
5. Without medicine for osteoporosis, I would be more likely to have broken bones than other people my age	○	○	○	○	○	○
6. My osteoporosis medicine reduces my risk of having broken bones	○	○	○	○	○	○
7. My osteoporosis medicine improves my chances of staying healthy	○	○	○	○	○	○

RISK OF FRACTURES FROM OSTEOPOROSIS

1. What do you believe the **Chance** is that you will have a fracture (broken bone) from osteoporosis over the next 10 years? (check one)

   ○ Very low chance
   ○ Low chance
   ○ Moderate chance
   ○ High chance
   ○ Very high chance

2. How **Susceptible** do you feel you are to having a fracture from osteoporosis over the next 10 years? (check one)

   ○ Not at all susceptible
   ○ Minimally susceptible
   ○ Mildly susceptible
   ○ Moderately susceptible
   ○ Highly susceptible
   ○ Very highly susceptible

3. What do you believe your chances are of having a fracture compared to other people your age and sex? (check one)

   ○ A lot lower
   ○ Lower
   ○ About the same
   ○ Higher
   ○ A lot higher

Please go to next page

HEALTH EFFECTS OF FRACTURES

(check one response for each item)	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
1. Having a hip or spine fracture would reduce my sense of well-being	○	○	○	○	○	○
2. Having a hip or spine fracture could reduce my health permanently	○	○	○	○	○	○
3. Having a hip or spine fracture may permanently limit my ability to do activities important to me	○	○	○	○	○	○

ABOUT YOUR OSTEOPOROSIS DOCTOR

Please think about the doctor who treats your osteoporosis as you answer these questions:

1. My doctor really cares about me as a person. (check one)

   ○ Totally disagree
   ○ Disagree
   ○ Neutral
   ○ Agree
   ○ Totally agree

2. My doctor is usually considerate of my needs and puts them first. (check one)

   ○ Totally disagree
   ○ Disagree
   ○ Neutral
   ○ Agree
   ○ Totally agree

3. I trust my doctor so much that I always try to follow his/her advice. (check one)

   ○ Totally disagree
   ○ Disagree
   ○ Neutral
   ○ Agree
   ○ Totally agree

4. If my doctor tells me something is so, then it must be true. (check one)

   ○ Totally disagree
   ○ Disagree
   ○ Neutral
   ○ Agree
   ○ Totally agree

5. I sometimes distrust my doctor's opinion and would like a second one. (check one)

   ○ Totally disagree
   ○ Disagree
   ○ Neutral
   ○ Agree
   ○ Totally agree

Please go to next page

6. I trust my doctor's judgment about my medical care. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

7. I feel my doctor does not do everything he/she should for my medical care. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

8. I trust my doctor to put my medical needs above all other considerations when treating my medical problems. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

9. My doctor is well qualified to manage (diagnose and treat or make an appropriate referral) medical problems like mine. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

10. I trust my doctor to tell me if a mistake was made about my treatment. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

11. I sometimes worry that my doctor may not keep the information we discuss totally private. (check one)

- ○ Totally disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Totally agree

Please go to next page

INFORMATION FROM YOUR OSTEOPOROSIS DOCTOR

How is the doctor or health care provider who treats your osteoporosis at:

(check one response for each item)	Poor	Fair	Good	Very good	Excellent
1. Telling you everything; not keeping things from you that you should know?	○	○	○	○	○
2. Letting you know test results when promised?	○	○	○	○	○
3. Explaining treatment alternatives?	○	○	○	○	○
4. Explaining side effects of medications?	○	○	○	○	○
5. Telling you what to expect from your treatment?	○	○	○	○	○

MAKING DECISIONS WITH YOUR OSTEOPOROSIS DOCTOR

1. Which of the following statements best describes your relationship **with the doctor who treats your osteoporosis**? (check one)

   ○ My doctor takes charge of my medical problems and tells me what I should do
   ○ My doctor tells me the options, and then we work as a team to develop a treatment plan
   ○ My doctor tells me the options, and then I decide what the treatment plan will be

2. How **Satisfied** are you with the way you and your doctor make decisions regarding your medical care? (check one)

   ○ Very dissatisfied
   ○ Dissatisfied
   ○ Satisfied
   ○ Very satisfied

HELP TAKING YOUR MEDICATIONS

If you do NOT currently take ANY prescription medications, you may skip this part and go on to the section "Taking Medications on Schedule" on page 8.

1. During the past month, how often did someone remind you to take your medication? (check one)

   ○ Never
   ○ Rarely
   ○ Sometimes
   ○ Often
   ○ Always

2. During the past month, how often did someone get your medication out and ready for you to take? (check one)

   ○ Never
   ○ Rarely
   ○ Sometimes
   ○ Often
   ○ Always

Please go to next page

3. During the past month, how often did someone encourage you to take your medication correctly? (check one)

   ○ Never
   ○ Rarely
   ○ Sometimes
   ○ Often
   ○ Always

4. During the past month, how often did someone give you practical tips to make it easier to take your medication? (check one)

   ○ Never
   ○ Rarely
   ○ Sometimes
   ○ Often
   ○ Always

TAKING MEDICATIONS ON SCHEDULE

Many every-day situations can make it difficult to take prescribed medications as you intend to take them. How confident are you that you will take your medications for osteoporosis under each of the following conditions?

1. You are feeling well? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

2. You are feeling ill? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

3. You are away from home? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

4. You are sad and blue? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

5. You have a busy day scheduled? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

6. No one reminds you to take the medicine? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

7. The schedule to take the medicine is inconvenient? (check one)

   ○ Not at all confident
   ○ Not very confident
   ○ Somewhat confident
   ○ Very confident
   ○ Totally confident

Please go to next page

DEPRESSION

1. In the past year, have you had 2 weeks or more during which you felt sad, blue or depressed; or when you lost all interest or pleasure in things that you usually cared about or enjoyed? (check one)

   ○ Yes
   ○ No

2. Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes? (check one)

   ○ Yes
   ○ No

3. Have you felt depressed or sad much of the time in the past year? (check one)

   ○ Yes
   ○ No

KNOWING ABOUT FRACTURES

1. Persons with osteoporosis (very low bone density) are at increased risk of suffering bone fractures (broken bones). (check one)

   ○ True
   ○ False
   ○ Don't know

2. **Hip** fractures usually permanently reduce ability to walk. (check one)

   ○ True
   ○ False
   ○ Don't know

3. If I fall and do not break a bone, I have a low risk of a future bone fracture even if I do have osteoporosis. (check one)

   ○ True
   ○ False
   ○ Don't know

4. Persons who suffer a broken bone from osteoporosis are at increased risk of having another one. (check one)

   ○ True
   ○ False
   ○ Don't know

5. Bone fractures in the **spine** do not cause chronic (permanent) back pain. (check one)

   ○ True
   ○ False
   ○ Don't know

6. A bone fracture in the **wrist** could cause permanent wrist pain. (check one)

   ○ True
   ○ False
   ○ Don't know

7. Bone fractures in the **spine** are a common cause of a bent over, curved back. (check one)

   ○ True
   ○ False
   ○ Don't know

8. Bone fractures in the **spine** rarely cause height loss. (check one)

   ○ True
   ○ False
   ○ Don't know

Please go to next page

9. **Hip** fractures can result in death. (check one)

- ○ True
- ○ False
- ○ Don't know

MORE ABOUT YOU

1. What is the highest grade or year of school you completed? (check one)

- ○ Some grade school or high school
- ○ High school graduate
- ○ Some college or vocational/trade school
- ○ 4-year college
- ○ More than 4-year college degree

2. Have you had any fractures in any of the following areas of your body? (check one response for each item)

	Yes	No
a. Hip……	○	○
b. Spine……..	○	○
c. Wrist……..	○	○
d. Upper arm or shoulder...	○	○
e. Pelvis……..	○	○

3. Have any of the following family members suffered a hip or spine fracture? (check one response for each item)

	Yes	No
a. Mother……..	○	○
b. Father……	○	○
c. Sister……..	○	○
d. Brother.....	○	○

4. Approximately what was your total household income last year before taxes? (check one)

- ○ $9,999 or less
- ○ $10,000 to $29,999
- ○ $30,000 to $59,999
- ○ $60,000 to $89,999
- ○ $90,000 or more

5. How would you describe yourself? (check all that apply)

- ○ Alaskan Native
- ○ American Indian
- ○ Asian or Pacific Islander
- ○ Black or African American
- ○ Hispanic
- ○ White
- ○ Other _____ (please specify)

6. The amount of money I have to pay each month for medications is a significant financial burden to me. (check one)

- ○ Strongly disagree
- ○ Disagree
- ○ Somewhat disagree
- ○ Somewhat agree
- ○ Agree
- ○ Strongly agree

Thank you for your help with this survey.

Please return the survey and the two consent forms in the enclosed postage-paid envelope to:

Beverly Gray
Park Nicollet Institute
Health Research Center
3800 Park Nicollet Blvd.
St. Louis Park, MN 55416

*Please take a minute to verify that you **completed ALL 10 pages** of this survey.*

Thank you.