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ORIGINAL RESEARCH

Structural equation modeling of the proximal–distal continuum of adherence drivers

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Objectives: Nonadherence to prescription medications has been shown to be significantly influenced by three key medication-specific beliefs: patients' perceived need for the prescribed medication, their concerns about the prescribed medication, and perceived medication affordability. Structural equation modeling was used to test the predictors of these three proximal determinants of medication adherence using the proximal–distal continuum of adherence drivers as the organizing conceptual framework.

Methods: In Spring 2008, survey participants were selected from the Harris Interactive Chronic Illness Panel, an internet-based panel of hundreds of thousands of adults with chronic disease. Respondents were eligible for the survey if they were aged 40 years and older, resided in the US, and reported having at least one of six chronic diseases: asthma, diabetes, hyperlipidemia, hypertension, osteoporosis, or other cardiovascular disease. A final sample size of 1072 was achieved. The proximal medication beliefs were measured by three multi-item scales: perceived need for medications, perceived medication concerns, and perceived medication affordability. The intermediate sociomedical beliefs and skills included four multi-item scales: perceived disease severity, knowledge about the prescribed medication, perceived immunity to side effects, and perceived value of nutraceuticals. Generic health beliefs and skills consisted of patient engagement in their care, health information-seeking tendencies, internal health locus of control, a single-item measure of self-rated health, and general mental health. Structural equation modeling was used to model proximal–distal continuum of adherence drivers.

Results: The average age was 58 years (range = 40–90 years), and 65% were female and 89% were white. Forty-one percent had at least a four-year college education, and just under half (45%) had an annual income of $50,000 or more. Hypertension and hyperlipidemia were each reported by about a quarter of respondents (24% and 23%, respectively). A smaller percentage of respondents had osteoporosis (17%), diabetes (15%), asthma (13%), or other cardiovascular disease (8%). Three independent variables were significantly associated with the three proximal adherence drivers: perceived disease severity, knowledge about the medication, and perceived value of nutraceuticals. Both perceived immunity to side effects and patient engagement was significantly associated with perceived need for medications and perceived medication concerns.

Conclusion: Testing the proximal–distal continuum of adherence drivers shed light on specific areas where adherence dialogue and enhancement should focus. Our results can help to inform the design of future adherence interventions as well as the content of patient education materials and adherence reminder letters. For long-term medication adherence, patients need to autonomously and intrinsically commit to therapy and that, in turn, is more likely to occur if they are both informed (disease and medication knowledge and rationale, disease severity, consequences of nonadherence, and side effects) and motivated (engaged in their care, perceive a need for medication, and believe the benefits outweigh the risks).

Keywords: compliance, prescription medications, medication beliefs, treatment beliefs

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Introduction

Over the past 40 years, numerous conceptual models have been proposed to explain medication nonadherence.[1] A short listing of models that have been tested in relation to medication adherence include the Health Belief Model,[2] the Theory of Reasoned Action,[3] the Theory of Planned Behavior,[4] the Transtheoretical Model,[5] the Necessity-Concerns Framework,[6] the Information-Motivation-Behavioral Skills model,[7] and the Information-Motivation-Strategy model.[8] Most of these frameworks belong to the family of models subsumed under social-cognitive theory,[1] and these models have incrementally built on the conceptual and empirical learning of one another. At the heart of all of these frameworks, as well as others, are two guiding assumptions: (1) individuals make decisions about prescription medications (ie, patients do not passively and reflexively obey physician recommendations about prescription medications); and (2) medication adherence is influenced by an array of patient beliefs, attitudes, skills, and experiences.

In 2009, the Proximal–Distal Continuum of Adherence Drivers model was proposed.[9] In the proximal–distal continuum, it was asserted that some adherence determinants are nearer or closer to patients' medication-taking decisions (proximal) while others are more removed (further from) patients' adherence decisions. The aim of the proximal–distal continuum was to organize the numerous hypothesized medication adherence drivers along an etiological continuum of determinants ranging from those shown to have strong empirical relationships with adherence (proximal drivers) to those with weaker relationships (distal drivers). In short, the proximal–distal continuum consists of an etiological hierarchy of hypothesized adherence drivers in order to account for medication adherence in a multifactorial manner.

The proximal–distal continuum is based upon three fundamental tenets. First, an adherent "personality" does not exist – the same individual can be adherent to one medication, not fill a second medication prescription, decide to stop taking a third medicine without the advice of their provider, and be careless taking a fourth medication.[9] A growing body of research has demonstrated that individual patients have different adherence patterns and levels for assorted medications, both within a therapeutic class[10–12] as well as across therapeutic areas.[13–16] Intraindividual variability in medication taking occurs because patients have different beliefs about different prescribed medications and their attendant diagnosed conditions. Second, patient beliefs, skills, and experiences that influence medication adherence can be either specific to a prescribed medication or disease

or they can be generic in nature (ie, nonspecific to a prescribed medication or disease). In general, patient beliefs, skills, and experiences specific to a prescribed medication or disease tend to be more predictive of adherence than generic psychosocial beliefs and skills.[9,17–21] Third, for many patients, a new diagnosis and the attendant prescribed therapy represents uncertainty and is a threat to the status quo.[22] The short-term benefits of prescription-medication therapy can seem intangible to patients, especially to those with asymptomatic chronic disease. The long-term benefits of prescription medications are probabilistic and can be so distant in the future that patients may heavily discount them. Viewed through the uncertainty lens, nonadherence can make sense from the patient perspective because taking prescription medications represents a risky prospect in the short term (short-term financial, psychological, and opportunity costs, and risk of side effects) with uncertain long-term benefits (probabilistic reductions in mortality, morbidity, and complications) compared to the status quo (health as it is).[23]

At the proximal end of the continuum are patients' beliefs about the prescribed medication (Figure 1). Research over the past 20 years has consistently demonstrated that patients' beliefs about a prescribed medication are potent predictors of medication adherence. Next, etiologically, are patients' sociomedical and disease-related beliefs, skills, and experiences which are hypothesized to be direct determinants of patients' proximal medication beliefs. Patients' generic beliefs, skills, and experiences are hypothesized to directly influence the disease-related and sociomedical beliefs. Finally, the most distal variables encompass demographic characteristics. Meta-analytic research has demonstrated weak associations between sociodemographic characteristics and adherence.[24]

A large body of research has provided evidence about the relative influence of the myriad adherence drivers potentially subsumed under the proximal–distal continuum. The vast majority of these studies have examined medication adherence as the outcome variable. However, few studies have modeled the determinants of proximal medication beliefs – beliefs demonstrated by past research to be powerful predictors of medication adherence. Nonadherence to prescription medications has been shown to be significantly influenced by three key medication-specific beliefs: patients' perceived need for the prescribed medication,[9,18,19,25–37] their concerns about the prescribed medication,[9,18,19,26,29,30,33,34,38–47] and perceived medication affordability.[9,48–55] We used structural equation
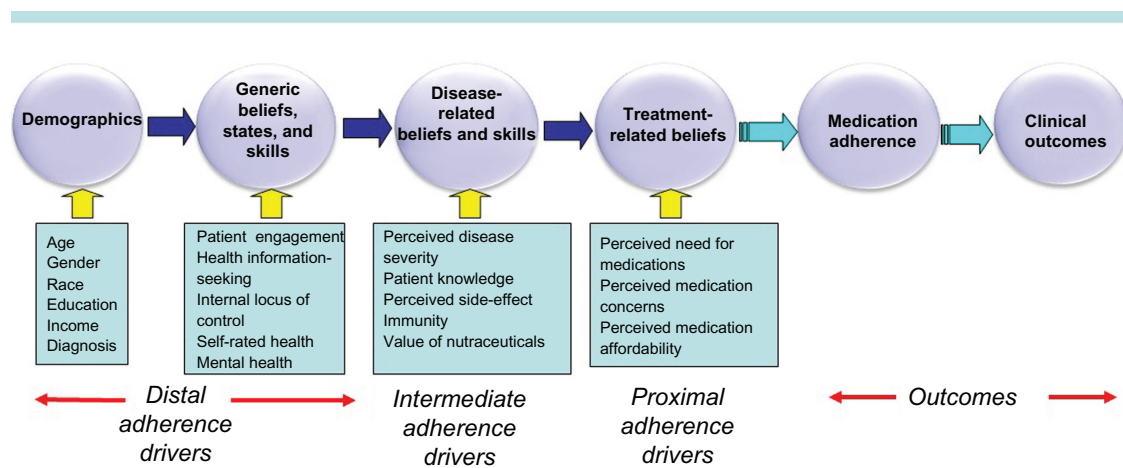
Figure 1 The proximal–distal continuum of adherence drivers.

modeling (SEM) to test the predictors of these three proximal determinants of medication adherence. The goal of testing the proximal–distal continuum was to shed light on the origins of the three key proximal medication beliefs. This information can contribute insights as to how future adherence interventions may be made more efficacious by identifying underlying mechanisms influencing perceived need for medications, perceived medication concerns, and perceived medication affordability.

Methods
Study design
Sampling procedure
As described in detail elsewhere,[9] in Spring 2008, survey participants were selected from the Harris Interactive Chronic Illness Panel, an internet-based panel of hundreds of thousands of adults with chronic disease. Respondents were eligible for the survey if they were aged 40 years and older, resided in the US, and reported having at least one of six chronic diseases prevalent among US adults: asthma, diabetes, hyperlipidemia, hypertension, osteoporosis, or other cardiovascular disease (CVD) (eg, angina, myocardial infarction, congestive heart failure). The six chronic diseases reflect a mix of symptomatic and asymptomatic conditions. They are some of the most highly prevalent conditions in the US[56] and are associated with a significant clinical and economic burden for the US health care system.[57] If eligible respondents reported more than one of the six target conditions, one was randomly selected as the index (study) disease. Panel members responding to an e-mail invitation were instructed to read the informed consent form and click on yes if they agreed to participate. The protocol for the survey was approved by the Essex Internal Review Board. A 26.5% survey contact rate

(per standards recommended by the American Association for Public Opinion Research)[58] was achieved. A total of 1072 adults completed the survey.

Survey content
The proximal, intermediate, and distal variables were all collected during a single survey administration. The proximal medication beliefs were measured by three multi-item scales: perceived need for medications (k = 12, Cronbach's alpha = 0.96, illustrative item: "I am convinced of the importance of my prescription medication.");[9] perceived medication concerns (k = 10, Cronbach's alpha = 0.90 items, illustrative item: "I worry that my prescription medication will do more harm than good to me.");[9] and perceived medication affordability (k = 7, Cronbach's alpha = 0.97, illustrative item "I feel financially burdened by my out-of-pocket expenses for my prescription medication.").[9] The intermediate disease-related and sociomedical beliefs and skills included four multi-item scales: perceived disease severity (k = 3, Cronbach's alpha = 0.76, illustrative item: "I think that my condition is severe."); knowledge about the index medication (k = 9, Cronbach's alpha = 0.92, illustrative item: "I understand exactly what the medication prescribed for me will do for me."); perceived immunity to side effects (k = 3, Cronbach's alpha = 0.90, illustrative item: "My chances of experiencing negative side effects from a prescription drug are high."); and perceived value of nutraceuticals (ie, vitamins, minerals, and supplements) (k = 7, Cronbach's alpha = 0.92, illustrative item: "For me personally, I believe that vitamin, mineral, and herbal supplements can achieve better health results than prescription drugs can."). Generic health beliefs and skills were measured by patient engagement in their care (k = 14, Cronbach's

alpha = 0.97, illustrative item "My doctor and I have a real partnership in my health care."); health information-seeking tendencies (k = 5, Cronbach's alpha = 0.91, illustrative item: "I actively seek out information on my illnesses."); internal health locus of control using Wallston's measure (k = 10, Cronbach's alpha = 0.89);[59] general mental health using the Mental Health Inventory (k = 5, Cronbach's alpha = 0.88);[60] and a single-item measure of self-rated health (the "excellent-to-poor" item from the Medical Outcomes Study [MOS] Short-Form Health Survey [SF-36]).[60] Evidence of the validity of these measures vis á vis the criterion of medication adherence has been previously published.[9,61–64] With the exception of the Mental Health Inventory (a six-point scale ranging from "all of the time" to "none of the time"), health locus of control (a six-point scale ranging from "strongly disagree" to "strongly agree"), and the "excellent-to-poor" item (excellent, very good, good, fair, or poor), all items used a six-point categorical rating scale ranging from "agree completely" to "disagree completely." Each multi-item scale was computed using Likert's method[65] of summated ratings in which each item is equally weighted and raw item scores are summed into a scale score. All scale scores were linearly transformed to a 0–100 metric, with 100 representing the most favorable belief or state, 0 the least favorable, and scores in between representing the percentage of the total possible score.

Demographic variables were included in the model. Age was measured as a continuous variable. Gender and race were coded as 1 = female vs 0 = male and 1 = white vs 0 = nonwhite, respectively. Education was measured as a six-level interval variable with higher values indicating higher education. Income was measured with an 11-level interval variable with higher values indicating higher income. Each disease indicator was coded as 1 = present vs 0 = not present with hypertension selected as the reference group because it had the largest sample size of the six diseases.

Statistical analysis
Survey noncontact analysis
Logistic regression was used to assess differences between Chronic Illness Panel members with valid e-mail addresses who did and did not respond to the survey invitation (ie, survey noncontact bias per standards recommended by the American Association for Public Opinion Research).[58] Independent variables for the logistic regression were age, gender, race, education, income, and geographic region of residence.

Structural equation modeling (SEM)
SEM was used in this analysis because some variables were both endogenous and exogenous, and traditional multivariate regression would not efficiently test the path relationships in one model. Twelve equations (three equations with the proximal beliefs as dependent variables, four equations with the intermediate beliefs and skills as dependent variables, and five equations with the generic beliefs, states, and skills as the dependent variables) were specified to represent the hypothesized relationships among the variables, which were treated as measured indicators of respondents' beliefs, states, and skills (see Figure 1). A single multivariate path model of these structural equations[66–69] was estimated by modeling the covariance matrix among the observed variables. As shown in Figure 1, the three proximal beliefs were specified to be associated with the intermediate, disease-related beliefs and skills, which in turn were associated with the distal generic beliefs and skills, and in turn with demographic characteristics.

SEM model fitting was performed in two steps. The first step was the execution of a full model to include all variables specified in the proximal–distal continuum (Figure 1). The final model, presented in Tables 2–4, includes only statistically-significant variables. Statistical significance, goodness-of-fit indices, and modification indices were used to guide the final model.

All available data were used in the analysis and were used as input into Mplus© software (version 6.1; Muthén and Muthén, Los Angeles, CA).[70] Full information maximum likelihood with the Mplus MLR estimator was used to estimate path coefficients and standard errors robust to nonnormality. The chi-square test and three fit indices (comparative fit index [CFI], root mean square error of approximation [RMSEA], and the standardized root mean square residual [SRMR]) provided an assessment of model fit. Good model fit was identified with chi-square ratio < 3.0, CFI > 0.95, RMSEA < 0.05, and SRMR < 0.08.[71] Correlated error terms were freely estimated within each domain (generic beliefs, intermediate beliefs, and proximal beliefs). Mplus uses model modification indices to determine what parameters should be added to the model to improve model fit. Modification indices are chi-square statistics with one degree of freedom for the fixed and constrained parameters in a structural equation model. They estimate the change in the improvement in the likelihood-ratio chi-square statistic for the model if the corresponding parameter is respecified as a free parameter. Modifications that improve model fit are regarded as potential changes that can be made to the

SEM model. The hypothesized relationships were tested based on their statistical significances of path coefficients.

Results

Survey noncontact

A 26.5% contact rate was achieved. Compared to those who were invited but did not respond to the survey, those successfully contacted were more likely to be age 55 and older, white, and college educated.[9]

Sample characteristics

As shown in Table 1, the average age of respondents was 58 years (range = 40–90 years), and 65% were female and 89% were white. Forty-one percent had at least a four-year college education and just under half (45%) had an annual income of $50,000 or more. Hypertension and hyperlipidemia were each reported by about a quarter of respondents (24% and 23%, respectively). A smaller percentage of respondents had osteoporosis (17%), diabetes (15%), asthma (13%), or other CVD (8%). A majority of the samples rated their health as good (39.1%) or fair (28.8%).

Results of SEM

Table 2 presents the standardized path coefficients from the SEM model for the proximal treatment beliefs. Goodness of fit indices showed good model fit with CFI = 0.973, RMSEA = 0.031 and SRMR = 0.032. The chi-square test was statistically significant (chi-square = 248, df = 121, $P < 0.0001$), reflecting a relatively good model fit[72] given the sample size and deviations from multivariate normality.[73–75] The model fit was much improved compared to the baseline full model (chi-square = 299, df = 24, RMSEA = 0.104) and an alternative model without considering modifications (chi-square = 324, df = 109, RMSEA = 0.043).

Greater perceived need for medications was related to greater perceived disease severity ($\beta = 0.480$), less value placed on nutraceuticals ($\beta = -0.249$), more knowledge about the index medication ($\beta = 0.244$), greater patient engagement in their care ($\beta = 0.137$), more perceived immunity to side effects ($\beta = 0.119$), and less information seeking ($\beta = -0.090$). In addition, age was positively related to perceived need for medications. Compared to patients with hypertension, those with dyslipidemia, osteoporosis, or other CVD perceived less need for the index medication. Over two-thirds (68.3%) of the variation in perceived need for medications was explained by these eight significant predictors.

Fewer medication concerns were associated with more perceived immunity to side effects ($\beta = 0.353$), less value placed on nutraceuticals ($\beta = -0.318$), more knowledge about the index medication ($\beta = 0.164$), greater patient engagement in their care ($\beta = 0.125$), less information seeking ($\beta = -0.084$), less perceived disease severity ($\beta = -0.078$), and less of an internal locus of control ($\beta = -0.051$). As age increased, medication concerns decreased. Compared to patients with hypertension, those with dyslipidemia or osteoporosis had more medication concerns. One-half (50.9%) of the variation in perceived medication concerns was explained by these nine significant predictors.

Better medication affordability was related to less perceived disease severity ($\beta = -0.233$), greater income

Table 1 Sociodemographic characteristics

Sociodemographic characteristic	N = 1072	
	N	%
Mean age (±SD)		58.3 (10.4)
Median age (±IQR)		58.0 (17.0)
Age 65+	325	30.3%
Female	695	64.8%
White	928	89.4%
Black	56	5.4%
Hispanic	30	2.9%
Other race	24	2.3%
Less than high school	12	1.1%
High school graduate	167	15.6%
Some college but no degree	450	42.0%
Bachelor's degree	177	16.5%
Some graduate school but no degree	88	8.2%
Graduate or professional degree	178	16.6%
Income < $15,000	62	6.8%
Income $15,000–$24,999	130	14.2%
Income $25,000–$34,999	149	16.3%
Income $35,000–$49,999	160	17.5%
Income $50,000–$74,999	177	19.4%
Income $75,000–$99,999	117	12.8%
Income $100,000–$124,999	49	5.4%
Income $125,000–$149,999	27	2.9%
Income $150,000–$199,999	22	2.4%
Income $200,000–$249,999	10	1.1%
Income > $250,000	11	1.2%
Asthma	144	13.4%
Diabetes	157	14.7%
Hyperlipidemia	249	23.2%
Hypertension	257	24.0%
Osteoporosis	180	16.8%
Other cardiovascular disease	85	7.9%
Self-rated health		
Excellent	20	1.9%
Very good	219	20.4%
Good	419	39.1%
Fair	309	28.8%
Poor	105	9.8%

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 2 Standardized path loadings of path model in predicting proximal beliefs

Independent variables	Proximal beliefs					
	Perceived need for medications		Perceived medication concerns		Perceived medication affordability	
	Standardized β	SE	Standardized β	SE	Standardized β	SE
Perceived disease severity	0.480‡	0.021	−0.078±	0.026	−0.233‡	0.030
Patient knowledge	0.244‡	0.031	0.164‡	0.032	0.082±	0.029
Perceived side-effect immunity	0.119‡	0.023	0.353‡	0.024	NS	NS
Perceived value of nutraceuticals	−0.249‡	0.025	−0.318‡	0.030	−0.222‡	0.029
Patient engagement	0.137‡	0.027	0.125‡	0.032	NS	NS
Information seeking	−0.090‡	0.021	−0.084±	0.027	NS	NS
Internal health locus of control	NS	NS	−0.051*	0.021	NS	NS
Self-rated health	NS	NS	NS	NS	0.136‡	0.032
Mental health	NS	NS	NS	NS	0.101±	0.031
Age	0.065‡	0.018	0.094‡	0.023	0.166‡	0.026
Female	NS	NS	NS	NS	−0.072±	0.026
White race	NS	NS	NS	NS	NS	NS
Education	NS	NS	NS	NS	0.057*	0.028
Income	NS	NS	NS	NS	0.231‡	0.031
Asthma	NS	NS	NS	NS	NS	NS
Diabetes	NS	NS	NS	NS	NS	NS
Lipid	−0.059‡	0.018	−0.053*	0.022	NS	NS
Osteoporosis	−0.081‡	0.020	−0.059±	0.022	NS	NS
Other CVD	−0.045±	0.017	NS	NS	NS	NS
R-square of model	0.683	0.016	0.509	0.023	0.340	0.023

Notes: ‡$P < 0.001$; ‡$P < 0.01$; *$P < 0.05$; goodness of model fit: P-values listed in parentheses; estimator = MLR; 127 free parameters; Chi-square = 248.122 (df = 121) with P-value < 0.0001; CFI = 0.973; RMSEA = 0.031; 90% CI = (0.026, 0.037); SRMR = 0.032.
Abbreviations: CVD, cardiovascular disease; NS, nonsignificant; SE, standard error; MLR, maximum likelihood with robust standard errors; CFI, comparative fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.

($\beta = 0.231$), less value placed on nutraceuticals ($\beta = -0.222$), older age ($\beta = 0.166$), better self-rated health ($\beta = 0.136$), better mental health ($\beta = 0.101$), and more knowledge about the index medication ($\beta = 0.082$). Females found medications to be less affordable, while education was positively related to perceived medication affordability. One-third (34.0%) of the variation in perceived medication affordability was explained by these nine significant predictors.

The four intermediate beliefs were then modeled as dependent variables (Table 3). Greater perceived disease severity was related to worse self-rated health ($\beta = -0.262$), greater patient engagement in their care ($\beta = 0.254$), greater information seeking ($\beta = 0.122$), and worse mental health ($\beta = -0.112$). As education increased, perceptions of disease severity decreased. Compared to patients with hypertension, those with asthma or osteoporosis perceived their diseases to be less severe, while those with other CVD and diabetes perceived their conditions to be more severe. One-quarter (25.1%) of the variation in perceived disease severity was explained by these six significant predictors.

Greater knowledge about the index medication was related to greater patient engagement in their care ($\beta = 0.521$), greater information-seeking tendencies ($\beta = 0.325$), more of

an internal locus of control ($\beta = 0.062$), and better mental health ($\beta = 0.047$). Close to one-half (47.7%) of the variation in knowledge about the index medication was explained by these four predictors.

Greater perceived immunity to side effects was associated with greater patient engagement in their care ($\beta = 0.259$), less information-seeking tendencies ($\beta = -0.242$), and better mental health ($\beta = 0.119$). Men felt more immune to side effects. As education increased, perceived immunity to side effects increased. Fifteen percent of the variation in perceived immunity to side effects was explained by these five predictors.

More value placed on nutraceuticals was associated with less patient engagement in care ($\beta = -0.415$), a greater internal locus of control ($\beta = 0.209$), greater information-seeking tendencies ($\beta = 0.126$), and better self-rated health ($\beta = 0.100$). Younger persons, nonwhites, and respondents with osteoporosis or asthma placed greater value on nutraceuticals compared to those with hypertension. As both education and income increased, value placed on nutraceuticals decreased. Over one-quarter (28.6%) of the variation in perceived value of nutraceuticals was explained by these predictors.

Table 3 Standardized path loadings of path model in predicting intermediate beliefs

Independent variables	Intermediate beliefs							
	Perceived disease severity		Patient knowledge		Perceived side-effect immunity		Perceived value of nutraceuticals	
	Standardized β	SE	Standardized β	SE	Standardized β	SE	Standardized β	SE
Patient engagement	0.254‡	0.029	0.521‡	0.023	0.259‡	0.030	−0.415‡	0.026
Health information seeking	0.122‡	0.028	0.325‡	0.026	−0.242‡	0.030	0.126‡	0.029
Internal health locus of control	NS	NS	0.062±	0.024	NS	NS	0.209‡	0.026
Self-rated health	−0.262‡	0.030	NS	NS	NS	NS	0.100‡	0.028
Mental health	−0.112‡	0.030	0.047*	0.021	0.119‡	0.029	NS	NS
Age	NS	NS	NS	NS	NS	NS	−0.084‡	0.025
Female	NS	NS	NS	NS	−0.111‡	0.027	NS	NS
White race	NS	NS	NS	NS	NS	NS	−0.053*	0.025
Education	−0.105‡	0.027	NS	NS	0.126‡	0.028	−0.083‡	0.028
Income	NS	NS	NS	NS	NS	NS	−0.122‡	0.029
Asthma	−0.074*	0.031	NS	NS	NS	NS	0.060*	0.026
Diabetes	0.130‡	0.026	NS	NS	NS	NS	NS	NS
Lipid	NS	NS	NS	NS	NS	NS	NS	NS
Osteoporosis	−0.103‡	0.029	NS	NS	NS	NS	0.128‡	0.025
Other CVD	0.094‡	0.026	NS	NS	NS	NS	NS	NS
R square for model	0.251	0.023	0.477	0.025	0.151	0.020	0.286	0.024

Notes: ‡$P < 0.001$; ±$P < 0.01$; *$P < 0.05$; goodness of model fit: P-values listed in parentheses; estimator = MLR; 127 free parameters; Chi-square = 248.122 (df = 121) with P-value < 0.0001; CFI = 0.973; RMSEA = 0.031; 90% CI = (0.026, 0.037); SRMR = 0.032.
Abbreviations: CVD, cardiovascular disease; NS, nonsignificant; SE, standard error; MLR, maximum likelihood with robust standard errors; CFI, comparative fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.

Determinants of the more distal generic beliefs are presented in Table 4. The more distal generic beliefs were predominately influenced by age and disease. Older adults and respondents with asthma were more engaged in their care compared to responders with hypertension ($R^2 = 0.037$). Greater information-seeking tendency was associated with female gender, more education, older age, and having asthma or other CVD compared to hypertension ($R^2 = 0.077$). Internal locus of control was associated with less education and nonwhite race ($R^2 = 0.014$). Better self-rated health was associated with higher income, older age, and a lower likelihood of other CVD or diabetes compared to hypertension ($R^2 = 0.121$). Finally, better mental health was associated with older age and higher income ($R^2 = 0.107$).

Discussion

Over the past 40 years, research on the determinants of medication adherence has gradually shifted from a focus on generic health beliefs to beliefs specific to a treatment and a disease. The Necessity-Concerns Framework[6] and Proximal–Distal Continuum[9] are two frameworks that hold that medication adherence is more powerfully explained by treatment-specific than by generic beliefs. Generic beliefs, in turn, are useful in understanding the determinants of disease-specific beliefs. To the best of the authors' knowledge, this is the first study that has concurrently modeled the predictors

of treatment-specific, proximal medication beliefs: perceived need for medications, perceived medication concerns, and perceived medication affordability.

Numerous hypotheses were tested in the SEM modeling of the proximal–distal continuum. However, only a few components of the proximal–distal continuum consistently emerged as statistically-significant predictors with relatively large path coefficients (perceived disease severity, patient knowledge, perceived side-effect immunity, perceived value of nutraceuticals, and patient engagement). These five variables are also the most clinically mutable beliefs and skills in the proximal–distal continuum. Because so few studies have studied the determinants of treatment-specific beliefs, we contextualize these results largely with past research on medication adherence and discuss their implications for adherence communication and adherence interventions.

Three of the intermediate, independent variables – perceived disease severity, knowledge about the index medication, and perceived value of nutraceuticals – were significantly associated with all three proximal adherence drivers. Perceived disease severity – or the potential for a condition to cause physical, mental or psychosocial harm – is a significant component of most social-cognitive models of medication taking.[2] Consistent with past research,[18–21,76,77] perceived disease severity was a significant predictor of the

Table 4 Standardized path loadings of path model in predicting distal beliefs

Independent variables	Distal beliefs									
	Patient engagement		Health information seeking		Internal health locus of control		Self-rated health		Mental health	
	Standardized β	SE	Standardized β	SE	Standardized β	SE	Standardized β	SE	Standardized β	SE
Age	0.169‡	0.027	0.070*	0.030	NS	NS	0.147‡	0.026	0.308‡	0.025
Female	NS	NS	0.218‡	0.030	NS	NS	NS	NS	NS	NS
White race	NS	NS	NS	NS	−0.069*	0.027	NS	NS	NS	NS
Education	NS	NS	0.127‡	0.029	−0.098‡	0.030	NS	NS	NS	NS
Income	NS	NS	NS	NS	NS	NS	0.245‡	0.027	0.121‡	0.029
Asthma	0.089‡	0.026	0.065*	0.026	NS	NS	NS	NS	NS	NS
Diabetes	NS	NS	NS	NS	NS	NS	−0.121‡	0.026	NS	NS
Lipid	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Osteoporosis	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Other CVD	NS	NS	0.096‡	0.027	NS	NS	−0.180‡	0.025	NS	NS
R square for model	0.037	0.010	0.077	0.016	0.014*	0.007	0.121	0.018	0.107	0.016

Notes: ‡$P < 0.001$; †$P < 0.01$; *$P < 0.05$; goodness of model fit: P-values listed in parentheses; estimator = MLR; 127 free parameters; Chi-square = 248.122 (df = 121) with P-value < 0.0001; CFI = 0.973; RMSEA = 0.031; 90% CI = (0.026, 0.037); SRMR = 0.032.
Abbreviations: CVD, cardiovascular disease; NS, nonsignificant; SE, standard error; MLR, maximum likelihood with robust standard errors; CFI, comparative fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.

three proximal treatment beliefs, but particularly of perceived need for medications. Patients who perceive their disease to be more severe may appreciate the long-term value of therapy, thus strengthening their intrinsic commitment to medication taking. Patients who perceive their disease to be more severe might be taking multiple medications, thereby making medications less affordable and raising concerns about medication side effects and medication interactions. Greater disease severity has been directly linked to improved medication adherence in numerous studies[78–82] including a meta-analysis.[83] Lack of perceived disease severity was cited as a reason for both medication nonfulfillment and nonpersistence in a study of US adults with chronic disease.[62] Patients need to understand the severity of their condition in order to internalize the rationale for therapy and develop ego commitment to the medication. Health care providers are uniquely qualified to convey to patients the potential severity of their conditions as well as short- and long-term consequences of undertreated or untreated chronic disease. Educational-based adherence interventions should explicitly address disease severity as a content area and assess patient understanding using well-established, patient-centered communication techniques.

In this study, patients with more knowledge about the index medication had significantly greater commitment to (need for) the medication, fewer medication concerns, and greater perceived medication affordability. The largest effect was observed for perceived need for the medication. Patient knowledge has been positively linked with medication adherence in many studies.[51,84–92] Information/knowledge is one of the troika of adherence drivers in two adherence conceptual frameworks – the Information-Motivation-Behavioral Skills model[7] and the Information-Motivation-Strategy model.[8] Lack of knowledge about the disease and/or prescribed therapy has been reported by patients as a reason for medication nonfulfillment or nonpersistence.[93–96]

Both qualitative[97–101] and quantitative[102–106] research has revealed that many patients lack knowledge about their diagnosed conditions, the potential severity of their conditions, and the consequences of lack of treatment. Patients also frequently report a lack of information about newly prescribed medications.[43,102,103,107–116] Without sufficient knowledge about their condition, its potential severity, and the rationale for the prescribed medication, many patients may find it difficult to identify with (be ego involved with) the diagnosis and therapy and to accept therapy with a sense of autonomous choice. When uncertainty and ambiguity are high, people tend to pessimistically evaluate the risk and benefits of therapy.[117]

Thus, lack of information and knowledge about the diagnosed condition and the prescribed therapy can exacerbate patients' uncertainty and ambivalence about prescription medications and can inhibit their internalization of their condition as chronic in nature.

Past educational/knowledge-based adherence interventions have tended to have small effect sizes.[118] This finding may be due to education and knowledge being operationalized and delivered differently across studies (eg, as disease knowledge, risk-factor knowledge, medication knowledge, and/or regimen knowledge) and the possibility that knowledge may more powerfully predict the proximal determinants of adherence –perceived need, concerns, and affordability – than adherence per se. Further, few adherence interventions have involved patients in the design and content of the intervention. Future adherence interventions should be truly patient-centered and involve patients a priori in determining what is needed, how much is needed, for how long, and via what channel. It is plausible that what newly diagnosed heart failure patients require in terms of information may be quantitatively and qualitatively different from what breast cancer patients newly prescribed adjuvant hormonal therapy need and prefer. Future adherence interventions should conceptualize knowledge in a multifactorial sense and deliver it longitudinally via a variety of channels and settings.[119]

Many past knowledge-based adherence interventions have been of short duration with only a handful or less of interventional touch points. Future adherence interventions should focus on the first two months of therapy, when the risk of nonpersistence is greatest. Multiple interventional touch points can reinforce learning and help minimize uncertainty. Disease knowledge (etiology, severity, course, and sequelae) and medication knowledge (rationale, duration of therapy, alternative therapies, risks and benefits, and consequences of nonadherence) need to be communicated in health–literacy appropriate ways. Such knowledge could be delivered with patient-centered decision aids or tools that attempt to present unbiased and complete information about the potential benefits and downsides of treatment choices.[120] The promise of patient-centered decision aids for prescription medications lies in the hope that, through their use, providers will be preparing patients for treatment and involving them in the treatment process. Patients may more readily and consistently accept treatment if they feel the decision to start therapy is their choice rather than the provider's directive.[121] Finally, it is important to underscore the difference between information/knowledge and patient understanding. Patients can only do what they understand.[8] Numerous patient-centered techniques are available to gauge patient understanding, such as "teach-back,"[122] "ask-tell-ask,"[123] and "elicit-provide-elicit."[124] These techniques could not only be used in adherence interventions but in routine clinical practice as well at the time of prescribing. In one study, physicians trained in ask-tell-ask were able to successfully employ the technique without statistically increasing the median visit length.[125]

A novel finding from this study is that respondents who placed more value on nutraceuticals (vitamins, supplements, and minerals) had lower perceived need for medications, more medication concerns, and less perceived medication affordability. Some adults believe over-the-counter and herbal remedies are less risky than prescription medications and that they are natural, safe, familiar, and can be used with less risk.[126–128] Gascon[100] found that there was greater confidence in herbal or natural remedies than in prescription medicines to treat hypertension. Other research has found use of complementary and alternative medicine (CAM) to be associated with suboptimal medication-effectiveness beliefs[129] and worse medication adherence.[130–134] Favorable attitude toward CAM has been reported to be associated with worse adherence intentions.[135] Thus, some adults may be substituting pharmaceuticals with nutraceuticals.

An uncertainty lens helps to explain why some patients migrate toward nutraceuticals and alternative medicine for the self-management of chronic disease – they are viewed as doing something good for oneself ("natural" remedies) and as actions involving little risk and little threat to the status quo. Internet website and print communications abound with advertisements that claim to treat or cure chronic disease naturally. Past research has shown that providers are not proactive in discussing nutraceuticals and CAM,[131,136] and that patients do not proactively disclose their nutraceutical and CAM use to their providers.[137,138] Physicians, pharmacists, and interventionists should proactively address use of nutraceuticals with patients and communicate their relative clinical efficacy for the treatment of chronic disease compared to prescription medications. Future research should better understand the role of nutraceuticals specifically, and CAM generally, in patients' adherence decisions.

Perceived side-effect immunity was a significant predictor of perceived need and perceived concerns but not affordability. Perceived side-effect immunity was the most important predictor of perceived medication concerns. Other research has linked perceived sensitivity to side effects with enhanced medication concerns.[6,77] Fear of side effects and

perceived side-effect susceptibility have been documented in the literature as reasons for medication nonadherence (nonfulfillment or nonpersistence)[62,139–145] and noncompliance (usage deviations).[146] Little is known about how or why patients come to feel susceptible to side effects. However, research has documented that patients report significant unmet need for side-effect information.[110,147–149] Physicians express concern that disclosure of side-effect information will increase patients' report and/or experience of side effects through the effect of suggestability.[150–154] However, extant research has refuted this line of reasoning: side-effect forewarning through verbal or written information has not been shown to increase reports of side effects.[155–161] On the contrary, patients have relayed that, armed with information about side effects, they would be less likely to become alarmed should a side effect occur and would have fewer concerns about them.[162–164] In one study, patients reported that detailed disclosure about side effects would make them feel more confident in the physician (94%), more likely to adhere to treatment (91%), and more confident in the medication (82%).[150]

Unaddressed medication concerns and fear of side effects can intensify patients' uncertainty especially when the potential benefits of medication therapy have not been appropriately communicated and when potential benefits do not occur immediately, as with most asymptomatic chronic conditions. Providers should disclose common side effects and create a plan with patients that addresses what they should do should a side effect occur.[165] Such collaborative communication behaviors are consistent with patient-centered care and shared decision making. Adherence interventionists can employ patient-centered decision aids to communicate both the pros and cons of treatment in a balanced manner.

Our measure of patient engagement assessed patient trust in their provider and patient involvement in their care. In this study, patient engagement was a significant predictor of six of the seven outcomes (all but perceived medication affordability). Patients who were more engaged in their care had a greater perceived need for medications, fewer medication concerns, perceived their disease to be more severe, had more knowledge about the index medication, felt more immune to side effects, and valued nutraceuticals less. The greatest impact was on prescription-medication knowledge. In women with osteoporosis, Schousboe et al[20] also found patient engagement to be significantly related to greater perceived need for medications and fewer medication concerns. Two other studies reported patient trust to be associated with better medication beliefs,[21,166] a finding similar to our observed results. Both patient trust[167–171] and patient involvement[172–174]

have been demonstrated in past research to be associated with improved medication adherence. Two recent meta-analyses concluded that better physician–patient collaboration[175] and better physician communication[176] significantly influence medication adherence.

Patient engagement is a key foundational element of patient-centered care and shared decision making. Past research has shown that patients can be coached to be more proactively involved in their care.[177–185] Involving patients in medication-therapy decision making may increase their intrinsic motivation and ego involvement in treatment. A simple way to engage patients is to ask whether they are ready to commit to therapy. Patients' expression of uncertainty or ambivalence is a marker for unresolved concerns or unmet information needs. Patient-centered decision aids for prescription medications may be a cost- and time-effective way of increasing patient engagement in their treatment in both clinical practice and in adherence interventions.

Although numerous hypotheses were tested in the SEM modeling of the proximal–distal continuum, none of the observed results were anomalous. In the vast majority of findings, coefficient signs were in the expected direction. As a predictor variable, the multi-item scale assessing health-information seeking yielded three results that could have plausibly been either positive or negative. Patients with greater health–information seeking tendencies had less perceived need for medications (Table 2), more perceived medication concerns, (Table 2), and less perceived immunity to side effects (Table 3). While health-information seeking was significantly and positively related to greater patient knowledge (Table 3), it is possible that health-information seeking could generate negative or even conflicting information, which could then dampen perceived need, elevate medication concerns, and elevate susceptibility to side effects.

Study strengths and limitations

There are both strengths and limitations to the study. In terms of strengths, use of the proximal–distal continuum was based upon both conceptual and empirical learning accumulated over the past 40 years. A large, internet-based panel of adults with chronic disease was accessed with representation from 47 of the 50 US states. Most of the multi-item scales were highly internally consistent (range of Cronbach's alpha of 0.76 to 0.97, median = 0.91). We had a large sample size (n = 1072) upon which to test the SEM model.

In terms of limitations, the survey contact rate (26.5%) was low. Survey noncontact analysis indicated that persons aged 55 years and older, whites, and those with at least a

college degree were more likely to be successfully contacted than their respective counterparts.[9] The obtained internet-based sample was slightly underrepresented by adults with income less than $25,000 annually compared to the US adult population.[186] Also, relative to the US adult population aged 25 years and older,[187,188] the obtained sample had an underrepresentation of adults with less than a high-school education, an overrepresentation of adults with at least a college degree, and overrepresentation of whites. Because of these demographic differences between the obtained sample and the US general adult population, generalizability of our results to the broader US population may not be appropriate. An Internet panel was used, which also may limit generalizability. The study was cross sectional. As a result of the cross-sectional design, no inferences regarding causality of the elements of the proximal–distal continuum can be made. The study involved adults with self-identified chronic disease. None of the six study conditions were substantiated with medical records. On the other hand, a well-defined, chronic disease panel was accessed and the six conditions were reverified using a separate, independent screener than was used to enroll the Chronic Illness Panel. Only six conditions were studied, although they are highly prevalent in the US adult population. No psychiatric conditions were studied. The array of adherence drivers tested in the proximal–distal continuum was not exhaustive of the 200 putative adherence determinants.[189] We did not study some adherence determinants included in other research, such as self-efficacy, social support, symptom severity, the experience of side effects, side-effect severity, length of time with the diagnosis, and length of time in treatment with prescription-medication therapy. We only tested the proximal–distal continuum and did not test alternative theoretical models of adherence drivers.

Conclusion

For decades now, nonadherence has been among the most significant problems facing medical practice.[190] Nonadherence is a psychosocial marker that issues important to patients were not addressed – that patients have unvoiced uncertainties and ambivalence about their condition and prescribed therapy. In clinical practice, a shroud of silence envelopes the topic of medication adherence: physicians often do not proactively ask about adherence and patients frequently do not tell them when they fail to fill a new prescription or stop therapy on their own.[9] Thus, patients are largely alone with their doubts and uncertainties. For long-term medication adherence, patients need to autonomously and intrinsically

commit to therapy and this is more likely to occur when they are informed (about disease knowledge, disease severity, medication knowledge and rationale, consequences of non-adherence, and side effects), understand, and are motivated (engaged in their care, perceive a need for medication, and believe the benefits outweigh the risks). In short, intuitively patient-centered strategies are needed to help patients to know what their condition is, why the medication is needed, how the prescribed therapy may help, and how the benefits may outweigh the risks.

Testing the proximal–distal continuum of adherence drivers sheds light on specific areas where adherence dialogue and enhancement could focus. Our results can help to inform the design of future adherence interventions, as well as the content of patient-education materials and adherence reminder letters. An important learning from testing the proximal–distal continuum is that future adherence interventions need to move from manipulating single adherence barriers to interceding in a multidimensional space. Results also suggest that intervening along the etiological continuum of patient beliefs, states, and skills may more optimally improve adherence than intervening in a single causal space. Interventions that focus on distal beliefs, states, and skills should be deprioritized. Instead of assuming a one-size-fit-all design, future adherence interventions should target persons who are deficit in the proximal determinants of adherence: perceived need for medications, perceived medication concerns, and perceived medication affordability. In addition, it should be possible to target patients or tailor interventions using the most important sociomedical predictors identified in this study: perceived disease severity, patient knowledge, perceived side-effect immunity, perceived value of nutraceuticals, and patient engagement.

Disclosure

The authors declare no conflicts of interest in this work.

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