Patient Preference and Adherence

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ORIGINAL RESEARCH

Measuring the Influence of Side Effect Expectations, Beliefs, and Incident Side Effects on the Risk for Drug Discontinuation Among Individuals Starting New Medications, a Cross-sectional Study

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Purpose: To measure the impact of beliefs, expectations, side effects, and their combined effects on the risk for medication nonpersistence.

Patients and methods: Using a cross-sectional design, individuals from Saskatchewan, Canada who started a new antihypertensive, cholesterol-lowering, or antihyperglycemic medication were surveyed about risk factors for nonpersistence including: (a) beliefs measured by a composite score of three questions asking about the threat of the condition, importance of the drug, and harm of the drug; (b) incident side effects attributed to treatment; and (c) expectations for side effects before starting treatment. Descriptive statistics and logistic regression models were used to quantify the influence of these risk factors on the outcome of nonpersistence. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

Results: Among 3,029 respondents, 5.8% (n=177) reported nonpersistence within four months after starting the new drug. After adjustment for numerous covariates representing sociodemographics, health-care providers, medication experiences and beliefs, both negative beliefs (OR: 7.26, 95%CI: 4.98–10.59) and incident side effects (OR: 8.00, 95%CI: 5.49–11.68) were associated with the highest odds of nonpersistence with no evidence of interaction. In contrast, expectations for side effects before starting treatment exhibited an important interaction with incident side effects following treatment initiation. Among respondents with incident side effects (n=741, 24.5%), the risk for early nonpersistence was 11.5% if they indicated an expectation for side effects before starting the medication compared to 23.6% if they did not (adjusted OR: 0.38, 95%CI: 0.25–0.60).

Conclusion: Expectations for side effects may be a previously unrecognized but important marker of the probability to persist with treatment. A high percentage of new medication users appeared unprepared for the possibility of side effects from their new medication making them less resilient if side effects occur.

Keywords: adherence, persistence, beliefs, attitudes, expectations

Introduction

Cardiovascular diseases consume a major portion of total health-care expenditures (ie, $350 billion annually in the USA).[1] Although increased use of risk-modifying medications has contributed to declining morbidity and health spending over the past two decades, adherence to these medications remains low.[2–5] Multiple studies have documented the high prevalence of nonadherence to cardiometabolic medications[2–5] resulting in poor risk factor control,[6,7]

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hospitalizations,[8,9] and potentially avoidable deaths.[10,11] Poor adherence can manifest in different ways. Individuals may skip doses during a course of therapy, often referred to as noncompliance[12] or poor implementation.[13] Alternatively, individuals may discontinue their drug altogether, an outcome known as nonpersistence.[12,13]

Nonpersistence to medications often occurs within days to weeks after the first dose.[4,14,15] Although side effects are considered a major cause of early nonpersistence,[16] the willingness to persist with a new medication is highly influenced by an individual's assessment of necessity versus concern.[17] A minor side effect may be unbearable for a person who believes their drug has few health benefits, while severe side effects may be tolerated by those believing their drug is essential. We previously found that negative medication beliefs were the most powerful predictors of early drug discontinuation among people experiencing side effects.[18] That is to say, patients with low confidence in their medication were more likely to discontinue it after a side effect occurred. Notably, expectations and beliefs can also influence the perception of side effects in addition to influencing the response to them.[19–23] However, it is unknown whether heightened perceptions of side effects (ie, the nocebo effect) will increase nonpersistence to a greater extent than that expected from negative beliefs alone. The practical relevance of these unresolved issues faces health-care providers daily. It could be argued that a prominent objective of many health-care providers is to inform individuals about side effects that should be expected.[24] Our research aim was to measure the impact of negative beliefs, expectations, incidents of side effects, and their combined effects on premature drug discontinuation (ie, nonpersistence).

Methods

Study data were from a population-based questionnaire mailed to residents in the province of Saskatchewan, Canada. The overall aim of the questionnaire was to capture adherence determinants that could be integrated with administrative databases to develop a comprehensive prediction model.[18] Saskatchewan has a universal drug insurance program that covers approximately 90% of the population of over one million residents regardless of age or socioeconomic status. All beneficiaries of the provincial drug insurance program were eligible to receive the questionnaire if they were at least 30 years old upon receiving a new claim for an antihypertensive, cholesterol-lowering, or antihyperglycemic medication between September 2019 and February 2020. To restrict the sample to new users only, eligible beneficiaries required at least two years of continuous provincial health coverage prior to the qualifying prescription without any prior claims for these eligible medications.[18] Permanent residents of long-term care facilities were not included. Screening for eligible beneficiaries was conducted on several occasions during the two year period; thus, questionnaires were mailed within four to six weeks of the earliest dispensation for one of these eligible medications. The mailout and consent form followed the Dillman strategy including an invitation letter, questionnaire package, and follow-up reminder.[25]

Participants

Respondents were included in the analysis if they: (a) confirmed receiving one of the eligible medications within the past four months; (b) returned a completed survey with a completed consent to participate; and (c) answered all items relating to persistence (one question), side effects (one question), and medication beliefs (three questions). Questionnaire design and dissemination have been described in detail elsewhere.[18] Briefly, the questionnaire contained 58 items designed to collect information on factors influencing adherence during the early phase of treatment including: patient-related factors (eg, knowledge, attitudes, beliefs), social and economic factors (eg, income, marital status), treatment-related factors (eg, side effects), and health-care system factors (eg, appointment length, relationship/trust/support).[18]

Seven of the questionnaire items were grouped into two composite scores developed previously: a knowledge score and health-care provider support score.[18] The first score represented health-care provider support and included five questions for a maximum of 25 points. Questions asked whether respondents were given a chance to ask the doctor questions, received information about side effects, the doctor spent time to help them understand, a nurse or pharmacist spent time, and if they trusted the doctor. Higher scores represented greater support from a health-care provider (Cronbach's alpha 0.82).[18] Also, a knowledge score was calculated from two questions asking whether they knew what the medication was used for and the reasons why the medicine was good for them (Cronbach's alpha 0.77).[18] Both scores were dichotomized into binary variables as described previously.[18]

Nonpersistence, Incident Side Effects, Expectations for Side Effects, and Beliefs

The primary outcome was nonpersistence, measured with the following question, "Are you still taking the new medicine prescribed to you?" (yes or no). Incidents of side-effects were identified by asking, "Did you experience side effect(s) from your new medicine?" (yes, no, not sure). Expectations for side effects was elicited by asking, "You expected to get side effects from this new medicine before you started taking it" (strongly agree, agree, not sure, disagree, strongly disagree).

Beliefs about medications were measured using three items with 5-point Likert scale response options ranging from strongly agree to strongly disagree. The first question asked about the "perceived threat of the medical condition" (ie, "Your new medicine is for a condition that is a danger to your health"). The second question focused on the "expected importance of the drug" (ie, "You are convinced that your new medicine is important for your health"), and the third asked about "perceived drug harms" (ie, "You worry that your new medicine will do more harm than good"). These questions were based on previously published questionnaires[17,26] and demonstrated concordance validity through a strong association with the risk of nonpersistence among a subgroup of respondents who experienced side effects in our previous study.[18] We calculated an overall beliefs score for each respondent based on the sum of responses to the three questions.[26] The beliefs score produced a total possible score of 15 points and a minimum of three points. Based on the overall beliefs score, individuals were dichotomized into "positive beliefs" and "negative beliefs" using the 25th percentile threshold (ie, score of <11 was considered "negative beliefs"). Cronbach's alpha[27] for the overall beliefs score was 0.68.

Statistical Analysis

We presented characteristics descriptively for the overall sample and for persistent and nonpersistent respondents using frequencies, percentages, means, standard deviations, and medians. Differences in characteristics between those reporting persistence and non-persistence were tested using chi-squared statistics.

Multivariable logistic regression models were used to assess the impact of beliefs, incident side effects, and expectations for side-effects on the outcome of nonpersistence in addition to the entire array of possible adherence predictors in the questionnaire. We fit a series of models in which all variables, other than age and sex, were first tested independently with the outcome and included in the final model only if they reached a significance level $P<0.10$ on univariate analysis and improved model discrimination performance determined by a statistically significant improvement in the integrated discrimination improvement statistic (IDI).[28] The final model also included age greater than 65 years and sex. None of the variables in the final model exhibited multicollinearity defined as a variance inflation factor of 2.5 or greater. We also tested a two-way interaction between side effects and beliefs to identify any statistical evidence of influence between these variables. We then tested the interaction between an "expectation for side effects" and incident side effects. Finally, we repeated the logistic regression analysis using individual beliefs questions rather than the overall beliefs score to ensure our results were not influenced by the decision to represent beliefs with a single score.

A c-statistic (ie, area under the receiver operating characteristic curve) was calculated for each model to assess overall discriminative performance.[29] Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. All analyses were conducted using SAS Software v9.4 (SAS Institute Inc., Cary, NC, USA). Our study was approved by the University of Saskatchewan Committee for Ethics in Human Research and complies with the Declaration of Helsinki.

Results

Out of 11,970 eligible individuals who were mailed a survey, 3,973 responded yielding a response rate of 33.2%. Of these, 3,029 (76.2%) reported starting new antihypertensive, cholesterol-lowering, or antihyperglycemic medication and answered all questions relating to side effects and beliefs (Figure 1). Respondents were equally distributed between males (49.7%) and females (49.5%) and the average age was 62.2 years (SD: 11.7 years). The majority of respondents were Caucasian (89.9%, n=2724), two-thirds had pursued formal education or training beyond high school (63.8%, n=1934), and over three-quarters were married or living with a partner (76.6%, n=2319). Most respondents listed general health status and mental health status as good to excellent (85.0% and 91.1%, respectively), and 82.9% (n=2510) earned more than $25,000 annually (CAD). Lipid-lowering medications were the most common new drug reported (53.5%, n=1620), followed by antihypertensives (28.9%, n=876), and antihyperglycemics (17.6%, n=533). Almost three quarters of

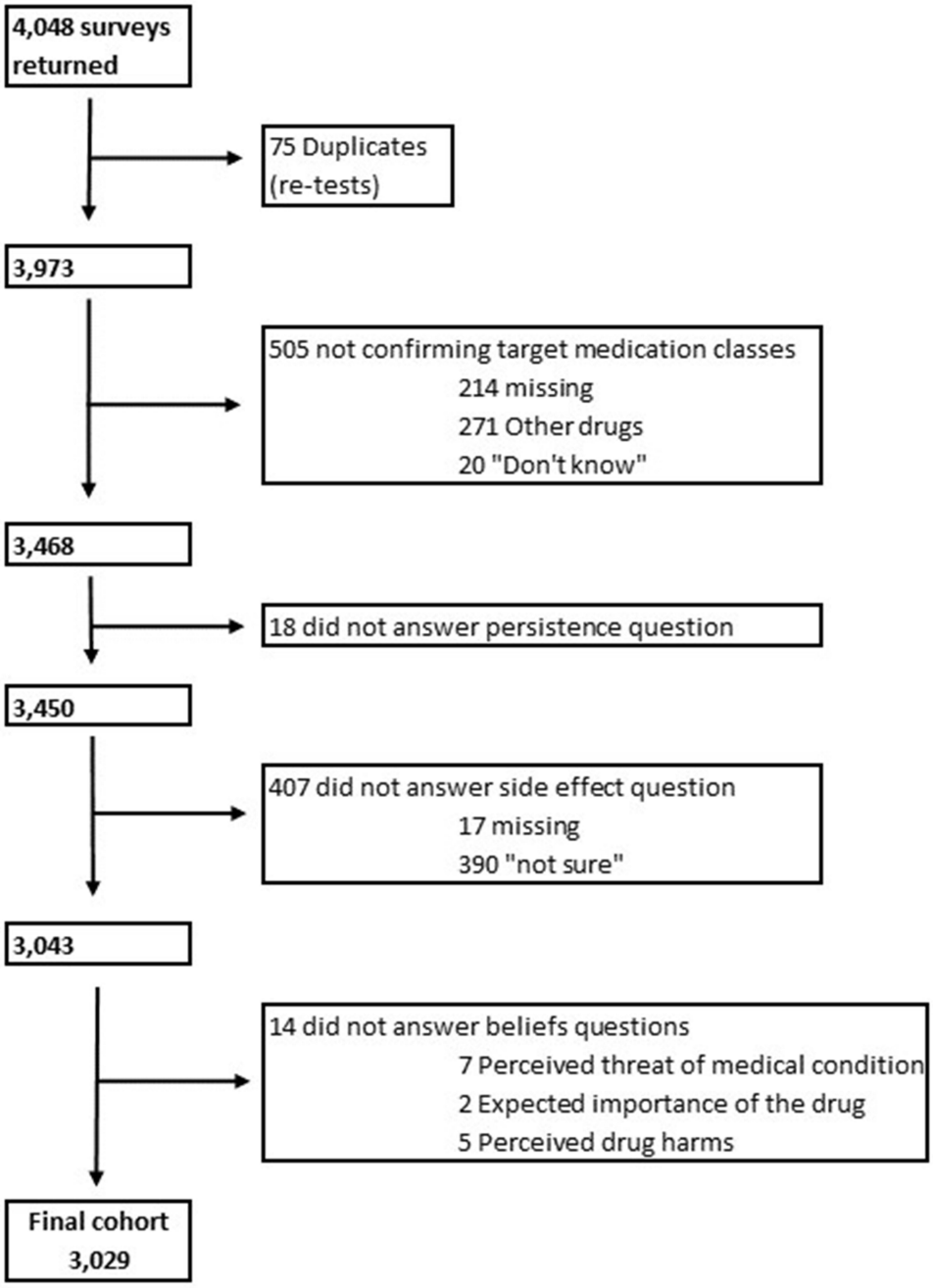

Figure 1 Flowchart for selection of study cohort.

patients received the prescription from their "regular doctor" (72.0%, n=2180) and 78.6% (n=2415) were taking two or more medications daily at the time of completing the questionnaire (Table 1).

Negative beliefs were expressed by only 1.8% to 10.2% of respondents in each of the three beliefs questions. The median overall beliefs score was 12 (range: 3–15) and respondents falling in the lowest quartile corresponded to a score <11 (17.2%, n=522). Incident side effects were reported by 24.5% (n=741). One quarter of respondents (25.8%, n=781) indicated they expected to get side effects from the new medicine before they started taking it.

Five variables were significantly associated with the outcome of nonpersistence based on the univariate model results: negative versus positive beliefs (21.5%, n=112 vs 2.7%, n=67, $P<0.001$) (Table 2); incident side effects vs no side effects (16.9%, n=125 vs 2.4%, n=54, $P<0.001$); expecting side effects before starting treatment (vs not expecting), (8.1%, n=63

Table 1 Characteristics of the Study Cohort

Variable	Overall, N=3029	Persistent N= 2826	Non-persistent N=177	P-value
Sex				0.236
Male	1,504 (49.7)	1,423 (50.4)	81 (45.8)	
Female	1,499 (49.5)	1,403 (49.6)	96 (54.2)	
Missing	26 (0.9)			
Age				0.736
<65	1,686 (55.7)	1,585 (56.1)	101 (57.4)	
≥65	1,316 (43.4)	1,241 (43.9)	75 (42.6)	
Missing	27 (0.9)			
Education				0.123
≤High school	1,081 (35.7)	1,008 (35.5)	73 (41.2)	
>High school	1,934 (63.8)	1,830 (64.5)	104 (58.8)	
Missing	14 (0.5)			
Race				0.003
Caucasian	2,724 (89.9)	2,576 (90.8)	148 (84.1)	
Other	289 (9.5)	261 (9.2)	28 (15.9)	
Missing	16 (0.5)			
Marital status				0.105
Married or living with partner	2,319 (76.6)	2,191 (77.6)	128 (72.3)	
Single, widowed, divorced	682 (22.5)	633 (22.4)	49 (27.7)	
Missing	28 (0.9)			
Total annual household income estimated for the past 12 months				0.009
≥ $25,000	2,510 (82.9)	2,375 (87.4)	135 (80.4)	
<$25,000	377 (12.4)	344 (12.7)	33 (19.6)	
Missing	142 (4.7)			
Do you get a discount on your medicine cost? Select "yes" if you do not pay full price.				0.724
Yes	2,094 (69.1)	1,972 (69.4)	122 (68.2)	
No or not sure	926 (30.6)	869 (30.6)	57 (31.8)	
Missing	9 (0.3)			
In the past few months, because of the cost, did you do anything to make your new medicine last longer?				0.005
Yes	54 (1.8)	46 (1.6)	8 (4.5)	
No or not sure	2,963 (97.8)	2,794 (98.4)	169 (95.5)	
Missing	12 (0.4)			
Did you go back to see your doctor to discuss the new medicine after you started taking it?				0.157
Yes	1,033 (34.1)	964 (34.6)	69 (39.9)	
No or not sure	1,926 (63.6)	1,822 (65.4)	104 (60.1)	
Missing	70 (2.3)			
Do you have a regular family doctor?				0.509
Yes	2,870 (94.8)	2,702 (95.0)	168 (93.9)	
No	154 (5.1)	143 (5.0)	11 (6.2)	
Missing	5 (0.2)			
Type of medication recently prescribed				0.675
Lipid lowering	1,620 (53.5)	1,525 (53.5)	95 (53.1)	
Antihyperglycemic	533 (17.6)	505 (17.7)	28 (15.6)	
Antihypertensive	876 (28.9)	820 (28.8)	56 (31.3)	
Medication prescribed in hospital				
Yes	389 (12.8)	367 (12.9)	22 (12.3)	0808
No	2,631 (86.9)	2,474 (87.1)	157 (87.7)	
Missing	9 (0.3)			

(*Continued*)

Table 1 (Continued).

Variable	Overall, N=3029	Persistent N= 2826	Non-persistent N=177	P-value
Number of prescribed medications daily				0.006
1	614 (20.3)	567 (20.0)	47 (29.0)	
2+	2,381 (78.6)	2,266 (80.0)	115 (71.0)	
Missing	34 (1.1)			
Your new medicine is difficult to take				<0.001
Strongly agree and agree	227 (7.3)	195 (6.9)	32 (17.9)	
Not sure	41 (8.0)	211 (7.4)	30 (16.8)	
Disagree and strongly disagree	2,554 (84.3)	2,437 (85.7)	117 (65.4)	
Missing	7 (0.2)			
You expected to get side effects from this new medicine before you started taking it.				0.032
Strongly agree and agree	781 (25.8)	718 (25.3)	63 (35.2)	
Not sure OR disagree and strongly disagree	2,242 (74.0)	2,126 (74.8)	116 (64.8)	
Missing	6 (0.2)			
In general, would you say your health is:				0.196
Excellent or very good	1,194 (39.4)	1,124 (39.6)	70 (39.1)	
Good	1,382 (45.6)	1,310 (46.1)	75 (41.9)	
Fair/poor	444 (14.7)	407 (14.3)	37 (20.7)	
Missing	9 (0.3)			
In general, would you say your mental health is:				0.541
Excellent or very good	1,865 (61.6)	1,746 (61.4)	119 (66.5)	
Good	894 (29.5)	850 (29.9)	44 (24.6)	
Fair/poor	264 (8.7)	248 (8.7)	16 (8.9)	
Missing	6 (0.2)			
Physical active				0.611
Yes	2,193 (72.4)	2,063 (73.0)	130 (74.7)	
No	809 (26.7)	765 (27.1)	44 (25.3)	
Missing	27 (0.9)			
Healthy diet				0.861
Yes	2,770 (91.4)	2,606 (92.0)	164 (91.6)	
No	242 (8.0)	227 (8.0)	15 (8.4)	
Missing	17 (0.6)			
Tobacco use				0.228
Daily or occasional use	382 (12.6)	354 (12.4)	28 (15.6)	
Non use	2,642 (87.2)	2,491 (87.6)	151 (84.4)	
Missing	5 (0.2)			
Health-care provider support score (median)				<0.001
≤16	1,421 (46.9)	1,301 (46.5)	120 (67.4)	
>16	1,558 (51.4)	1,500 (53.6)	58 (32.6)	
Missing	50 (1.7)			
Knowledge about medications				<0.001
≥7	1,904 (62.9)	1,822 (64.1)	82 (46.3)	
<7	1,114 (36.8)	1,019 (35.9)	95 (53.7)	
Missing	11 (0.4)			

vs 5.2%, n=116, P=0.032), a low (vs high) knowledge score (less than seven vs higher than six, (8.5%, n=95 vs 4.3%, n=82, P<0.001); and a low health-care provider score (less than 17 vs higher than 16, 8.4%, n=120 vs 3.7%, n=58, P<0.001). The influence of side effects and beliefs on the risk for nonpersistence were consistent regardless of the presence of each other. (Table 2) The highest risk of nonpersistence was observed in people expressing both negative

Table 2 Frequency and Percentage of Respondents Expressing Beliefs, Side Effects, and Nonpersistence

Item (s)	Response (s)	Percent of Total Group (n=3029) (N)	Percent Exhibiting nonpersistence (ie, Row Percentage) (n)	Percent of all Nonpersistence Cases Reported in Total Group (ie, Column Percentage with Denominator = 179) (N)	Percent Experiencing Side Effects (ie, Row Percentage) (N)	Percent Exhibiting nonpersistence Among those with Side Effects (N)	Percent Exhibiting nonpersistence Among those Without Side Effects (N)
Worry that medication will do more harm than good	Negative belief (ie, agree or strongly agree)	10.2 (309)	30.7 (95)	53.1 (95)	55.3 (171)	43.9 (75)	14.5 (20)
	Positive belief (ie, disagree, strongly disagree, or unsure)	89.8 (2720)	3.1 (84)	46.9 (84)	21.0 (570)	8.8 (50)	1.6 (34)
Convinced medication is important for your health	Negative belief (ie, disagree, strongly disagree, or unsure)	1.8 (55)	61.8 (34)	19.0 (34)	63.6 (35)	74.3 (26)	40.0 (8)
	Positive belief (ie, agree or strongly agree	98.2 (2974)	4.9 (145)	81.0 (145)	23.7 (706)	14.0 (99)	2.0 (46)
Medication is for danger condition	Negative belief (ie, disagree, strongly disagree, or unsure)	4.9 (148)	16.2 (24)	13.4 (24)	31.1 (46)	37.1 (17)	6.9 (7)
	Positive belief (ie, agree or strongly agree)	95.1 (2881)	5.4 (155)	86.6 (155)	24.1 (695)	15.5 (108)	2.2 (47)
Overall beliefs score derived from 3 questions above	Negative beliefs (<11)	17.2 (522)	21.5 (112)	62.6 (112)	40.4 (211)	38.9 (82)	9.7 (30)
	Positive beliefs	82.8 (2507)	2.7 (67)	37.4 (67)	21.1 (530)	8.1 (43)	1.2 (24)

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Table 3 Odds Ratios and 95% Confidence Intervals for Logistic Regression Analysis of Risk Factors Associated with Medication Nonpersistence

Variable	Odds Ratio (unadjusted)	95% Confidence interval		P-value	Odds Ratio (adjusted)[a]	95% Confidence interval		Pvalue
Female (vs male)	1.20	0.89	1.63	0.237	1.06	0.75	1.50	0.747
Age 65 or older (vs <65 years)	0.95	0.70	1.29	0.736	1.03	0.72	1.46	0.889
Knowledge score <7 (vs 7 or higher)	2.07	1.53	2.81	**<0.001**	1.07	0.71	1.60	0.756
Health-care provider score <17 (vs 17 or higher)	2.39	1.73	3.29	**<0.001**	1.16	0.76	1.78	0.487
Expectation for side effects prior to starting medication (yes vs no)[b]	1.61	1.17	2.21	**0.003**	[b]	[b]	[b]	0.211
Beliefs score <11 (vs 11 or higher)	9.95	7.22	13.70	**<0.001**	7.26	4.98	10.59	<0.001
Side effects (yes vs no)[b]	8.40	6.03	11.69	**<0.001**	[b]	[b]	[b]	<0.001
Interaction term (side effects and expectation for side effects before starting therapy)	–	–	–	–	–	–	–	<0.001

Notes: [a]Odds ratios are adjusted for all variables in the table (sex, age, knowledge score, health-care provider score, expectation for side effects, beliefs score, side effects, and the two way interaction term). [b]OR suppressed due to the significant interaction between expectation for side effects and actual side effects.

beliefs and side effects at the same time (38.9%, n=82), while the risk for nonpersistence was extremely low in people without either risk factor (1.2%, n=24) (Table 2).

Side effects were reported more frequently in respondents with negative beliefs (ie, 40.4% when beliefs score <11 vs 21.1% when score was 11 or higher, $P<0.001$). Side effects were also reported more commonly by those who expected them before starting the new medication (55.4% vs 14.7%, $P<0.001$).

Variables entered in the multivariable logistic regression model included age, sex, and the five variables significantly associated with early nonpersistence in univariate models: knowledge score, health-care provider score, expectation for side effects, beliefs, and incident side effects (Table 3). In the final model, three variables were significantly associated with nonpersistence: (1) negative beliefs (ie, overall beliefs score <11): (OR: 7.47, 95%CI: 5.13–10.86); (2) incident side effects: (OR 8.00, 95%CI: 5.49–11.68); and (3) expectations for side-effects before starting treatment: (OR: 0.57, 95%CI: 0.39–0.83).

No statistically significant interaction was detected between occurrence of side effects and beliefs. However, the two-way interaction between the expectation for side effects and incident side effects was significant; thus, the interaction term was included in the final model. The c-statistic for the final model containing the main effects plus the two-way interaction was 0.84.

Investigation of the significant interaction term revealed a potentially important effect modification. Among respondents with incident side effects, the risk for early nonpersistence was 11.5% if they indicated an expectation for side effects before starting the medication compared to 23.6% if they did not expect side effects prior to starting the drug (adjusted OR: 0.38, 95%CI: 0.25–0.60). A prior expectation for side effects was less important for those who did not experience side effects from their new drug (ie, 4.3 vs 2.0% for those expecting vs not expecting side effects, adjusted OR: 1.59, 95%CI: 0.85–2.98).

Discussion

We conducted a population-based survey study of individuals receiving a new medication from one of three common pharmacologic classes: antihypertensives, cholesterol-lowering, or antihyperglycemics. Negative beliefs and incident side effects were the strongest risk factors for early nonpersistence; their effects were additive but we found no evidence that they influence each other. Individuals with both side effects and negative beliefs exhibited the highest risk for nonpersistence while the absence of both factors virtually eliminated the risk. In contrast to beliefs, an expectation for

side effects before starting treatment appeared to protect against the negative influence of incident side effects. Specifically, those who expected side effects were half as likely to discontinue if side effects occurred. However, the majority of respondents expected no side effects before starting their new medication.

People who expect side effects are considered more likely to exhibit negative beliefs about medications and also more likely to experience nocebo effects. A nocebo effects is defined as an "amplified perception of benign sensations" based on knowledge or anxiety about a given drug.[19] Those who do not expect side effects are generally considered optimistic and accepting of medication therapy.[19,20,22,23,30] Although we found a higher incidence of side effects among those who expected them, the results of our study provide a very different perspective about the potential influence of side effect expectations on the risk for nonpersistence.

According to our results, an expectation for side effects may play a role in preparing some people for tolerability issues during the early stages of therapy. In contrast, expecting no side effects before starting a new medication could be an inconspicuous risk factor for nonpersistence. It is not clear why our results appear to conflict with research about nocebo effects; however, studies examining nocebo effects tended to be performed in highly controlled conditions, often with healthy volunteers responding to hypothetical situations.[30] Our population was drawn from real world patients initiating a medication for a chronic condition. Furthermore, knowledge about side effects has been associated with high medication adherence previously,[31] and patients have indicated that side effect information is important to help inform their own treatment decisions.[32]

If side effect expectations do provide some protection against the risk for nonpersistence, it is important to note that only one quarter of our respondents expected side effects before starting their new drug. This result was somewhat unexpected given the widespread public awareness of drug adverse effects[33] and attention given to health-care provider communication.[24] However, when counseling patients on medication adverse effects, physicians and pharmacists are often focused on reducing fear in order to facilitate positive attitudes.[24,34,35] Perhaps these well-intentioned priorities are instilling false expectations among patients that side effects will not occur. Our study suggests that practitioners should ensure patients understand that side effects are a real possibility, which may not be clear if patient education is overly optimistic.

Limitations

We conducted a rigorous analysis of patient-reported risk factors for nonpersistence. However, several limitations must be noted. First, our data was derived from voluntary responders to a population-level study invitation. Thus, we cannot be certain the aggregate experiences collected from our study sample reflect population averages. For example, the low frequency of negative beliefs observed in our sample may have been influenced by a healthy responder bias.[36] Despite this limitation, we found clear associations between negative beliefs and side effects with nonpersistence to medications that we believe exist in the general population. Second, our questionnaire was developed for maximum breadth of potential adherence risk factors. To minimize responder fatigue, we collected important factors such as negative beliefs using abbreviated measures in many cases. Our approach produced two important disadvantages, it reduced the potential granularity of our analysis relating to the major sub-scales of the beliefs paradigm (ie, necessity, concern, overuse, and harm);[37] it also potentially reduced the validity of the measure given the reliance on a very limited number of questions. However, we had high confidence in the clarity and face validity of our beliefs questions. In addition, the association between our questions about side effects, beliefs, and expectations were very strong and allowed for a clear assessment of impact and interaction with a wide range of other factors. Third, the cross-sectional design of our study made it impossible to confirm temporal relationships between beliefs, starting the new drug, and emergence of side effects. Thus, we can only speculate about the true nature of the associations reported in this study. Fourth and finally, all our data were self-reported. Thus, we cannot verify the accuracy and honesty of respondents to vital questions such as "Are you still taking the medicine prescribed to you" (ie, our primary endpoint). However, we have confidence in the clarity and importance of discontinuing medication as a definitive and relevant outcome.

Conclusion

Prior to starting a new medication, an individual's expectations for side effects may be a previously unrecognized but important marker of their probability to persist with treatment. A high percentage of new medication users appear unprepared for the possibility of side effects from their new medication making them less resilient if side effects occur.

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