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Frequency of and reasons for medication non-fulfillment and non-persistence among American adults with chronic disease in 2008

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Abstract

Objective To identify self-reported reasons why adults with chronic disease do not fill a new prescription (medication non-fulfillment) and/or stop taking a medication without their physician telling them to do so (lack of medication persistence).

Methods Participants were sampled in 2008 from a national, internet-based panel of American adults with chronic disease. A total of 19 830 respondents answered questions about medication non-fulfillment and medication non-persistence and reasons for non-fulfillment and non-persistence. Among persons self-identified as non-fulfillers and non-persisters, statistical analyses assessed the association between reported reasons for non-fulfillment and non-persistence and chronic disease. A subsample of respondents completed an additional survey which included multi-item scales assessing matched constructs of most of the reasons for non-fulfillment and non-persistence. The convergent validity of the self-reported reasons was assessed against the multi-item scales.

Results The same four reasons were most commonly reported for both medication non-fulfillment and medication non-persistence: paying for the medication a financial hardship (56 and 43%, respectively); fear or experience of side effects (46 and 35%, respectively); generic concerns about medications (32 and 23%, respectively); and lack of perceived need for the medication (25 and 23%, respectively). The frequency with which the reasons were reported varied somewhat by chronic disease. The convergent validity of most of the self-reported reasons was confirmed against multi-item scales measuring matched constructs.

Conclusions The same top reasons for medication non-fulfillment and non-adherence were observed in a large internet-based sample of American adults with chronic disease. Future efforts to improve medication adherence should address patients' medication concerns, perceived need for medications, and perceived medication affordability.

Introduction

Adherence to prescription medications for chronic disease is a problem of international proportion. Approximately one half of adults who begin a new therapy for chronic disease become non-persistent in the first year of therapy.[1,2] This statistic holds true for acute and chronic conditions as well as symptomatic and asymptomatic conditions. Across 36 studies of patient populations,[3] a median of 17.2% of patients did not fill a new prescription (also referred to as primary non-adherence or medication non-fulfillment), and the same median statistic for 23 studies involving general populations was 11.5%.[3] The widespread nature of medication non-fulfillment and non-persistence, and the fact that they know no demographic, geographic, or political boundaries, has spurred researchers and clinicians to design and evaluate interventions to improve adherence to prescription medications. The first review of adherence interventions appeared in 1985.[S1] Since then, many different meta-analyses,[S2–S4] systematic reviews,[S5–S7] and narrative reviews[1,S8–S10] have been published on adherence interventions. The overarching conclusion of this bolus of work is that adherence interventions have only had modest effects on persistence with prescribed medication therapy.

On the one hand, the atheoretical nature of some adherence interventions has been cited as a reason for their weak results.[S11] On the other hand, recent recommendations have underscored that adherence interventions might be strengthened if they were developed from evidence-based determinants of adherence and were patient-centred in content, i.e. based on patients' reasons for non-adherence.[S7,S11–S13] A direct way to achieve patient-centredness is to solicit from patients themselves their reasons for failing to fill a new prescription and their reasons for discontinuing therapy without their provider telling them to do so.[S14] Few interventions have been conceptualized and executed with such a patient-centric rationale.

Qualitative research has described reasons for non-fulfillment and non-persistence from the patient perspective, but with their attendant limitations on sample size and generalizability. Myriad survey studies exist on reasons for non-fulfillment and non-persistence, but they vary greatly in the breadth and depth of the methodology used to elicit the reasons as well as the representativeness of the obtained samples. What has been gleaned from this research to date? The following factors have been reported to influence medication non-fulfillment: lack of perceived need for the medication,[4–17] concerns about side effects,[6,10,12,16,18,19] poor expectations for drug efficacy,[9,10,12–14,16,18] medication costs,[4,5,7,9,11–14,16–21,S15] poor understanding of the illness,[20] perceived polypharmacy (i.e. taking too many drugs),[13] general aversion to medications,[16] unaware a prescription was written,[4–6,8,9,18,19] forgot to pick up the prescription,[5,6,8,11,13–15,18] too busy to pick up the prescription,[6,7,10,14,15] transportation issues/inconvenient pharmacy location,[6,11,12,16,18,19,21] and long waits at the pharmacy.[6,15,18,21] A similar inventory of reasons has been reported to influence non-persistence given the initial prescription was filled: unconvinced of the need for the medication,[22–33] experience of side effects,[12,22–24,26–29,31–43,S16–S18] fear of side effects,[24,30,32,38,40,44,45] long-term medication-safety concerns,[26,29,30,40,46] lack of perceived medication effectiveness,[23,27,29,30,33,36,38,41,44,47] medication costs,[12,22,27–29,37,38,43,45] lack of health insurance,[22] general aversion to medications,[24,30,33,43] feeling worse as a result of the treatment, [25] feeling well or better,[23,25,33,39,46–48] poorly informed disease-aetiology beliefs,[27] unclear and/or complicated instructions,[38] time consuming, difficult, or inconvenient regimen,[29,34,38,44,45] doubts about the provider's competence,[35] having no health care provider,[22] preferring life-style modification to medications,[31,32] forgetfulness,[22–25,27,34,37,42,44,48,S19] interference with daily routines,[27,38] and perceived polyphamacy.[25,32,48]

While large in volume, existing research on reasons for non-fulfillment and non-persistence can be characterized by several limitations. First, virtually all extant research has focused on a single therapeutic area. Only one study assessed

reasons for non-persistence across multiple therapeutic areas.[27] Second, only one study has examined reasons for non-fulfillment as well as non-persistence.[12] Third, because of the diverse methodologies utilized, it is impossible to prioritize which of the inventoried reasons for non-fulfillment and non-persistence play the most influential role in patients' decisions to forgo their prescribed therapy.

In this study, we elicited from adults with chronic disease their reasons for failing to fill a new prescription for one of five chronic diseases as well as their reasons for stopping prescription medication therapy without their providers instructing them to do so. The outcome of this research should prove to be informative to adherence researchers who seek to design adherence interventions consonant with patient-centred reasons for medication non-fulfillment and non-persistence.

Methods

Subject selection

As described in detail elsewhere,[49] survey participants were selected from the Harris Interactive Chronic Illness Panel (CIP), a nationally representative, internet-based panel of hundreds of thousands of American adults with chronic disease. In the spring of 2008, 165,487 members of Harris's CIP were sent an e-mail invitation to participate in the survey. The subject of the e-mail invitation was 'Survey about Health Issues in America.' Neither in the e-mail invitation nor in the informed-consent form did the communication indicate the study was about prescription medications. Respondents were eligible for the survey if they were aged 40 and older, resided in the USA, and reported having at least one of six chronic diseases: asthma, diabetes, hyperlipidaemia, hypertension, osteoporosis, or other cardiovascular disease. Panel members responding to the e-mail invitation were instructed to read the informed-consent form and click on *yes* if they agreed to participate. The protocol for the study was approved by the Essex IRB.

Definition of medication non-fulfillment and non-persistence

To identify respondents as non-fulfillers, the survey asked if, in the last year, they had received, but did not fill, a new prescription from their healthcare provider for one of the six target conditions. If respondents endorsed *yes*, they were presented with a list of 10 reasons why adults might not fill a new prescription medication (see Table 1 for item content) and asked to choose all that applied to them. To identify respondents as non-persisters, the survey asked if, in the last year, they had stopped taking a prescription medication for one of the six conditions without their providers telling them to do so. If respondents answered *yes*, they were presented with a list of 12 reasons why adults might stop taking their medications (see Table 1 for item content) and asked them to choose all that applied to them.

As described in detail elsewhere,[49] a subset of the respondents who were identified as non-fulfillers and non-persisters completed a 102-item questionnaire assessing a variety of medication beliefs as well as perceived disease severity and patient knowledge about their condition. This subset was sampled sequentially until preset quotas were met.[49]

Statistical analysis

Survey non-contact bias

As described elsewhere,[49] logistic regression was used to assess differences between selected CIP panel members with valid e-mail addresses who did and did not respond to the survey invitation. Independent variables were age, gender, race, education and income.

Reasons for medication non-fulfillment and non-persistence

The frequency of medication non-fulfillment was calculated among respondents reporting a new prescription in the previous year. The frequency of medication non-persistence in the previous year was calculated among respondents who were currently taking prescription medications

Table 1 Proportion reporting reasons for non-fulfillment and non-persistence, stratified by disease

		Disease					
Reason for non-fulfillment	All, % $N = 265$	Asthma, % $N = 48$	Diabetes, % $N = 36$	Hyperlipidaemia, % $N = 79$	Hypertension, % $N = 49$	Osteoporosis, % $N = 53$	P^1
Paying for medication was a financial hardship	55.8	58.3	69.4	44.3	61.2	56.6	0.089
Fear of side effects	46.4	33.3	25.0	64.6	34.7	56.6	< 0.001
Concerns about taking the medication	32.5	18.8	19.4	43.0	28.6	41.5	0.006
Did not think needed the medication	25.3	39.6	22.2	26.6	18.4	18.9	0.136
Change in health insurance/benefit	18.1	12.5	22.2	10.1	24.5	26.4	0.021
Did not believe condition was life-threatening	17.0	14.6	8.3	20.3	8.2	28.3	0.027
Fear of drug interactions	10.6	6.3	5.6	11.4	10.2	17.0	0.348
Did not think medication would work/be effective	8.3	8.3	2.8	7.6	10.2	11.3	0.478
Inconvenient/complex dosing regimen	6.0	4.2	2.8	5.1	4.1	13.2	0.393
Did not understand the medication's purpose	3.4	2.1	2.8	1.3	4.1	7.5	0.533
Reason for Non-Persistence	$N = 2935$	$N = 716$	$N = 448$	$N = 742$	$N = 692$	$N = 337$	
Paying for medication was a financial hardship	43.0	44.0	40.6	40.6	46.2	43.0	0.096
Experience or fear of side effects	34.8	21.5	34.8	47.2	27.7	49.9	< 0.001
Concerns about taking the medication	23.1	18.6	22.1	29.2	17.1	32.9	< 0.001
Did not think needed the medication	22.7	39.4	18.5	14.8	23.4	8.9	< 0.001
Change in health insurance/benefit	17.7	16.8	17.4	15.6	21.7	16.3	0.007
Did not believe condition was life-threatening	13.4	19.1	9.2	12.8	10.3	14.8	< 0.001
Problems remembering to take medication	12.2	14.0	12.5	8.2	13.3	14.8	< 0.001
Did not see evidence medication was working	11.4	10.2	13.6	9.6	12.1	13.6	0.090
Experience or fear of drug interactions	7.6	6.1	6.7	9.2	6.9	9.5	0.110
Did not think medication would work/be effective	5.5	7.0	5.6	4.7	4.9	5.3	0.433
Inconvenient/complex dosing regimen	4.1	3.8	4.7	2.0	2.6	11.3	< 0.001
Did not understand the medication's purpose	1.1	0.7	1.6	0.5	1.7	1.5	0.137

[1]Test of association between reason and disease, adjusted for lack of independence.

and/or had stopped taking a medication without their provider telling them to do so. The univariate distribution for all of the non-fulfillment and non-persistence reasons was tabulated.

The invariance of the non-fulfillment and non-persistence reasons across chronic disease was assessed using logistic regression with generalized estimating equations (GEE)[S20] to adjust for the lack of independence among respondents who were non-fulfillers or non-persisters for more than one disease.

The original reasons for non-fulfillment and non-persistence were subsequently collapsed into five omnibus reasons: medication concerns (side effects, generic concerns, drug interactions), lack of perceived need for medications (did not think needed, did not believe condition was life threatening, did not understand the purpose of the medication), perceived medication affordability (financial hardship and health insurance), lack of perceived medication benefits (did not think would be effective and did not see evidence was working), and regimen difficulties (dosing regimen and problems remembering). The most-frequently endorsed combinations of reasons was tabulated.

Convergent validity of self-reported reasons for non-fulfillment and non-persistence

Convergent validity refers to the degree to which scores on a measure are related to scores on other measures that are designed to assess the same construct. We conducted two tests of convergent validity. First, self-reported income and relative income (compared to all US households) should be a reasonable proxy for the non-fulfillment and non-persistence reason of financial hardship. It was hypothesized that respondents with less income and lower relative income would be more likely to cite financial hardship as reasons for non-fulfillment and non-persistence. This hypothesis was tested using a proportional-odds regression model with GEE[S20] to adjust for the lack of independence among respondents who were non-fulfillers or non-persisters for more than one disease. In these models, income and relative-income categories were treated as ordinal variables.

Second, it was hypothesized that respondents citing a given reason for non-fulfillment or non-persistence should score statistically lower on a content-relevant, multi-item scale than those not citing said reason. These hypotheses were tested using *t*-tests. The reasons related to financial hardship and health insurance were compared against multi-item scales measuring perceived medication affordability and cost-related medication under-use. The reasons about fear or experience of side effects, general medication concerns, and fear of drug interactions were evaluated against multi-item scales measuring side-effect concerns and medication-safety concerns. The reasons regarding lack of perceived need for medications, did not understand the purpose of the medication, and did not believe condition was life threatening were judged against multi-item scales measuring perceived need for medications, patient knowledge about the prescribed medication, and perceived disease severity. There were no matched multi-item scales assessing the reasons related to perceived treatment benefit (did not think the medication would work and did not see evidence the medication was working), and regimen difficulties (dosing regimen and problems remembering to take the medication).

As described elsewhere,[49] the multi-item scales were computed by summing raw items into a scale score and linearly transforming each sum to a 0–100 metric, with 100 representing the most favourable belief, 0 the least favourable, and scores in between representing the percentage of the total possible score.[49] The multi-item scales were highly reliable, with Cronbach's alpha coefficients ranging from 0.76 to 0.97 (median of 0.91). All statistical analyses were conducted using SAS 9.1.2 (SAS Institute Inc., Cary, NC, USA).

Results

Survey contact and sample restrictions

Figure S1 depicts the flow of subjects through sample eligibility. Among the 165 487 invitations sent, there were 15 035 invalid e-mail

addresses. Of the 150 452 invitations with valid e-mail addresses, 39 874 persons provided informed consent and entered the survey screen (26.5% contact rate). Compared to those who were invited but did not respond, those successfully contacted were more likely to be age 55 and older, Caucasian, and college educated.[49]

Of the 39 874 who entered the survey, 20 299 (50.9%) met the study qualification criteria (age 40 or older, US resident, and one of the six conditions), and 19 830 met the inclusion criteria for one or more data analyses. Responses for persons with other cardiovascular disease were excluded from all analyses because a small number of respondents ($n = 408$) indicated they had that diagnosis. An additional 60 respondents were excluded due to inconsistent or missing data. Before analysing reasons for non-fulfillment or non-persistence, an additional 52 non-fulfillers and 287 non-persisters were excluded because they did not provide an analyzable reason.

Sample characteristics

As shown in Table S1, a majority of the non-fulfillers and non-persisters were female (72 and 67%, respectively) and 87% were self-identified as Caucasian. Respondent age ranged from 40 to 96 years (mean and median age of 59.4 and 59, respectively). Over one-third of respondents reported at least a 4-year college degree (34% non-fulfillers and 38% non-persisters), and over 40% (40% non-fulfillers and 46% non-persisters) of those providing income reported an annual household income ≥$50 000. Over two-thirds of respondents rated their health as fair or good.

Frequency of medication non-fulfillment and non-persistence

Among the 7365 respondents who had received at least one new prescription in the last year, 291 respondents (4.0%) reported not filling at least one prescription. Non-fulfillment was highest for those with osteoporosis (12.5%), lowest for those with diabetes (1.8%) or hypertension (2.0%), and intermediate for those with asthma (4.6%) or hyperlipidaemia (4.9%).

Among the 19 794 respondents eligible for the non-persistence analysis, 2756 (13.9%) reported non-persistence for at least one prescription in the previous year. Non-persistence was highest for those with osteoporosis (20.0%) and asthma (17.0%), lowest for those with hypertension (5.9%), and intermediate for those with diabetes (8.0%) or hyperlipidaemia (11.0%).

Reasons for medication non-fulfillment and non-persistence

As shown in Table 1, the same top six reasons were observed for both medication non-fulfillment and non-persistence: financial hardship (56 and 43%, respectively); fear or experience of side effects (46 and 35%, respectively); generic concerns about medications (32 and 23%, respectively); lack of perceived need for the medication (25 and 23%, respectively); change in health insurance or drug benefits (18 and 18%, respectively); and did not believe that their condition was life threatening (17 and 13%, respectively). Only 12% of the non-persisters cited problems remembering to take the medication as a reason for non-persistence.

Table 1 also shows the distribution of reasons by disease. Among the non-fulfillers, six of the ten reasons were statistically invariant across the five diseases. Side-effect concerns and generic medication concerns were reported most frequently among those not filling a medication for hyperlipidaemia (65 and 43%, respectively) and osteoporosis (57 and 42% respectively) and least frequently among non-fulfillers for diabetes medications (25 and 19% respectively). Respondents with osteoporosis were 3.5 times more likely to endorse 'did not think condition was life threatening' as a reason for non-fulfillment compared to persons with diabetes and hypertension.

Among the non-persisters, five of the 12 reasons were statistically invariant across the five diseases. Side-effect concerns and generic medication concerns were reported most frequently

among those stopping a medication for osteoporosis (50 and 33%, respectively) and hyperlipidaemia (47 and 29%, respectively). Respondents with asthma were the most likely to answer they did not think they needed the medication (39%) and they did not think their condition was life threatening (19%). Respondents with osteoporosis were four times more likely to cite problems with the regimen as a reason for non-persistence (11%) compared to those with hyperlipidaemia and hypertension.

As shown in Table S2, for those reporting only a single omnibus reason for non-fulfillment, the most common barrier was affordability (33%), medication concerns (15%) and lack of perceived need (7%). The most common combinations of reasons were affordability with medication concerns (13%) and medication concerns with lack of perceived need (11%). For those reporting only a single reason for non-persistence, the most commonly cited reasons were affordability (29%), medication concerns (21%) and lack of perceived need (9%). The most common combinations of reasons were affordability with medication concerns (5%), medication concerns with lack of perceived need (5%), and affordability with lack of perceived need (3%).

Convergent validity of reasons for non-fulfillment and non-persistence

Are respondents who report less income and less relative income more likely to cite financial hardship as reasons for non-fulfillment and non-persistence? The proportion reporting financial hardship as a reason for non-fulfillment ranged from 70% among those with household income <$25 000 to 27% among those with income ≥$100 000 ($P = 0.009$). For non-persisters, the proportion reporting financial hardship ranged from 60% among those with household income <$25 000 to 22% among those with income ≥$100 000 ($P < 0.0001$). The proportion reporting financial hardship as a reason for non-fulfillment ranged from 68% of those reporting their relative income to be less than half of all US households to 15% of those reporting their relative income to be more than double that of all US households ($P = 0.005$). For non-persisters, the proportion reporting financial hardship ranged from 60% of those reporting their relative income to be less than half of all US households to 21% of those reporting their relative income to be more than double that of all US households ($P < 0.0001$).

Table S3 presents the convergent validity results for the reasons related to change in insurance/drug benefits and financial hardship. Consistent with the hypotheses, non-fulfillers and non-persisters who attributed their non-adherence to a change in health insurance/drug benefits had significantly lower scores on the multi-item scales assessing perceived medication affordability and cost-related medication under-use compared to those not endorsing those reasons. Non-fulfillers and non-persisters reporting financial hardship as a reason scored one standard deviation lower on the perceived medication affordability and cost-related medication under-use scales. The observed associations were stronger among non-persisters than non-fulfillers.

As shown in Table 2, for both non-fulfillers and non-persisters, reporting the reasons of experience or fear of side effects or generic medication concerns was associated with significantly lower scores on the multi-item scales assessing side-effect concerns and medication-safety concerns. Reporting experience or fear of drug interactions was associated with significantly lower scores for medication-safety concerns for both non-fulfillers and non-persisters. Non-persisters who cited experience or fear of drug interactions also scored significantly lower on the scale assessing side-effect concerns. All of the observed associations were stronger among non-persisters than non-fulfillers.

Reporting lack of perceived need for the medication and did not believe the condition was life threatening were both associated with significantly lower scores for perceived need and perceived disease severity scales among non-fulfillers and non-persisters (Table 3). Among non-fulfillers, the multi-item scale assessing patient knowledge of their prescribed medica-

Table 2 Convergent validity related to prescription medication concerns among non-fulfillers (N = 236) and non-persisters (N = 927)

	Side-effect concerns (k = 5)[1]		Medication-safety concerns (k = 5)[1]	
	Mean score	t-value	Mean score	t-value
Reason for non-fulfillment				
Fear of side effects a reason				
Yes	39.6	7.57[2]	37.7	3.69[3]
No	61.6		49.0	
General concerns about medications a reason				
Yes	36.2	7.18[2]	36.2	3.43[3]
No	58.9		47.5	
Fear of drug interactions a reason				
Yes	44.8	1.71	33.3	2.70[4]
No	52.9		45.6	
Reason for non-persistence				
Experience or fear of side effects a reason				
Yes	45.5	11.18[2]	44.4	4.54[2]
No	63.3		51.8	
General concerns about medications a reason				
Yes	44.6	7.97[2]	39.8	6.68[2]
No	59.4		51.5	
Experience or fear of drug interactions a reason				
Yes	36.4	7.16[2]	37.9	3.96[2]
No	57.4		49.6	

k = number of questionnaire items in the multi-item scale.
[1]Higher scores represent more favourable beliefs: fewer side-effect concerns and fewer medication-safety concerns.
[2]$P < 0.0001$; [3]$P < 0.001$; [4]$P < 0.01$.

Table 3 Convergent validity related to prescription medication need among non-fulfillers (N = 236) and non-persisters (N = 927)

	Perceived need for medications (k = 12)[1]		Perceived disease severity (k = 3)[1]		Patient Knowledge (k = 9)[1]	
	Mean score	t-value	Mean score	t-value	Mean score	t-value
Reason for non-fulfillment						
Did not think needed the medication						
Yes	47.7	4.32[2]	40.8	4.30[2]	75.8	−0.55
No	64.1		58.4		74.4	
Did not think condition was life threatening						
Yes	45.5	4.07[2]	41.3	3.27[3]	76.6	−0.63
No	63.2		56.9		74.4	
Did not understand the purpose of the medication						
Yes	63.5	−0.42	60.6	−0.77	66.9	1.35
No	60.1		54.0		75.1	
Reason for non-persistence						
Did not think needed the medication						
Yes	53.9	4.76[2]	41.1	6.76[2]	71.9	1.17
No	64.7		56.3		74.9	
Did not think condition was life threatening						
Yes	53.2	6.32[2]	43.7	5.70[2]	72.2	2.58[4]
No	66.2		57.1		76.5	
Did not understand the purpose of the medication						
Yes	57.2	1.10	56.7	−0.21	67.6	1.60
No	64.4		55.1		76.0	

k = number of questionnaire items in the multi-item scale.
[1]Higher scores represent more favourable beliefs: better perceived need for medications, less perceived disease severity, and better patient knowledge.
[2]$P < 0.0001$; [3]$P < 0.001$; [4]$P < 0.05$.

tion was not associated with any of the reasons for non-fulfillment. Among non-persisters, the patient knowledge scale was only associated with perceived disease severity as a reason for non-persistence. Among both non-fulfillers and non-persisters, none of the multi-item scales were associated with the reason of did not understand the purpose of my medication.

Discussion

In an internet-based survey of American adults with five common chronic diseases, the frequency of self-reported non-fulfillment was 4.0%. Rates of prescription non-fulfillment have been documented to vary dramatically in the literature (from 0.2 to 57.1%) for several reasons:[3] (i) different medications studied; (ii) different time periods studied (from 1980 to 2007); (iii) widely varying sample sizes (from <20 to over 45 000); and (iv) differential representativeness of the obtained samples (e.g. patients sampled from single medical practices, hospitals, and retail pharmacies as well as nationally representative surveys of general populations). Further, a major problem confounding comparison of non-fulfillment rates is that there is not an agreed-upon definition of non-fulfillment. As a result, non-fulfillment has been asked in a variety of ways[3] (e.g. did you or a family member not fill a prescription, did you delay filling a prescription or not fill it at all, and did you not fill or refill due to costs) using different reference periods[3] (from 3 days to 2 years) and different methodologies[3] (from self-report to pharmacy

claims). Finally, the unit of analysis has varied across studies[3] – most studies report the percentage of patients not filling a prescription, but others report the percentage of prescriptions not filled or a ratio of unfilled to filled prescriptions.

If our observed non-fulfillment rate is compared to studies of persons with chronic disease or those sampled at health care facilities, then our rate of 4.0% is below the median of 17.2% derived across 36 peer-reviewed studies.[3] However, two recent news releases reported primary non-adherence in US health plans to be 6.8% in 2008[S21] and 6.3 in 2009.[S22] Our observed rate could be lower than the median of 17.2% for several reasons. First, we studied adults with five chronic diseases while other studies included both children and adults with chronic disease.[3] Second, other studies sampled from primary care facilities, hospitals, and emergency rooms[3] while our sampling frame was a chronic-disease internet panel. Third, it is unknown the extent to which self-report errors (under-reporting or over-reporting of medication taking) were operative among our respondents as well as those in the other studies. Fourth, it is plausible that some patients in our sample (obtained in 2008) had their prescriptions transmitted to the pharmacy by electronic prescribing, fax, or telephone, thereby making them unaware that a prescription was written, which would result in under-reporting of non-fulfillment. In one non-fulfillment study involving e-prescriptions, 28% of respondents claimed that they were unaware that a prescription was ordered.[9] Fifth, some studies used pharmacy-claims data to derive non-fulfillment estimates.[3] If these studies were not conducted in closed-pharmacy systems, patients could have redeemed their prescriptions at other pharmacies, thereby leading to overestimates of non-fulfillment. Finally, it is plausible that there was differential survey response in our study by medication fulfillment status. According to leverage-salience theory,[S23] survey response will be greater when the survey topic is of special interest or relevance to potential sample members. Although the e-mail invitation did not specify the content of the survey, aside from 'Survey about Health Issues in America,' we cannot rule out the possibility of differential survey response by medication fulfillment status, which would have biased our observed non-fulfillment rates downward if fulfillers had higher survey response rates than non-fulfillers.

In our internet-based survey of American adults with five common chronic diseases, the frequency of self-reported non-persistence in the previous year was 13.9%, which is below the 20–50% 1-year non-persistence rate commonly reported in the literature.[1,2] A similar inventory of plausible explanations can account for differences in non-persistence rates across studies: different diseases and medications studied across different time periods with extensively varying sample sizes obtained from widely varying sampling frames using different data collection techniques and different operational definitions of non-persistence. Studies analysing pharmacy refill claims will overestimate non-persistence if patients: (i) switch retail pharmacies in open-pharmacy systems; (ii) switch to mail-order refills from retail pharmacies; and (iii) switch to another in-class medication and such switches are classified as non-persistence. Importantly, many non-persistence studies limit the sampling frame to patients new to therapy, who are the most likely to be non-persistent with therapy.[S24] Since we did not limit sample eligibility to patients who were treatment naïve, our observed estimate of non-persistence is likely biased downward. Our observed estimate of non-persistence would also be biased downward if medication persisters had higher survey response rates than medication non-persisters.

Among respondents reporting medication non-fulfillment and non-persistence, three predominant reasons were observed – perceived medication affordability, perceived medication concerns and lack of perceived need for medications. Across the five diseases, non-fulfillers had a higher frequency of citing financial hardship as a reason compared to non-persisters (56 vs. 43%). Non-fulfillers were more likely to name side-effect concerns (46 vs. 35%) and generic medication concerns (32 vs. 23%) than were non-persisters. Non-fulfillers and non-persisters had roughly the same frequency of citing

lack of perceived need for medications (25 vs. 23%) and did not think condition was life threatening (17 vs. 13%).

Our observed results on perceived medication concerns and lack of perceived need for medications are consistent with published research[49,S25–S40] which has demonstrated that medication non-adherence is influenced by two key patient beliefs about their prescription medication therapy: concerns about medications and perceived need for medications. Our findings that both non-fulfillers and non-persisters most-frequently cited medication costs as a reason for their behaviours is consistent with recent US research on cost-related non-adherence[S41] and cost-related medication under-use.[S42]

Our results pertaining to perceived medication affordability should alert researchers and policy makers to seek mechanisms to make prescription medications more affordable for consumers, perhaps via value-based benefit design, which has been discussed as a potential avenue for policy intervention.[S43] Research has documented the impact of reduced out-of-pocket costs for prescription medications on improved adherence[S44–45] and reduced payer costs.[S44] However, making medications more affordable is not a panacea for non-adherence. Countries which offer more generous prescription drug benefits than the USA do not have better medication adherence. For example, van Wijk and colleagues[S46] demonstrated striking similarity in non-persistence rates to antihypertensive therapy in the USA, British Columbia, and the Netherlands. Other research has documented remarkable similarity of medication non-adherence across counties with different prescription drug benefits.[S47–S51] Further, the adherence enigma is not as simple as out-of-pocket costs. When patients view a medication as essential, they often find the means to afford it.[S52–S53] When patients do not perceive a need for medications or have concerns about the prescribed medication, making them more affordable will likely not move the adherence needle.[S54] Research has demonstrated that the price elasticity between copayments and adherence is small,[S55–S57] i.e., reductions in out-of-pocket prescription drug spending result in small increases in the demand for prescription medications. This occurs because non-adherence is influenced by factors other than costs, as suggested by the analyses presented herein. In our previous work,[49] perceived medication affordability was the most prevalent adherence driver studied but was the less impactful than perceived need for medications and perceived medication concerns in differentiating medication persisters from non-fulfillers and non-persisters.

The reasons related to forgetfulness and lack of understanding of the purpose of the medication were cited infrequently by the self-reported non-persisters (12 and 1%, respectively). Many past adherence interventions have focused either on practical barriers (by addressing forgetfulness with reminders devices) or knowledge barriers via various educational interventions. Our observed results, however, suggest that these approaches may be relevant for a minority of patients. Our results, should they prove to be replicable, suggest that perceptual barriers related to perceived medications concerns, perceived need for medications, and perceived medication affordability represent the next natural content focus for adherence interventions.

Only 6% of the non-fulfillers and 4% of the non-persisters attributed regimen difficulty or complexity as reasons for non-fulfillment and non-persistence. Research has clearly demonstrated improvements in adherence associated with less frequent dosing[S58] as well as fixed-dose combinations.[S59] It is possible that the respondents to our survey were prescribed less onerous medication regimens, thereby rendering the medication regimen reason of lesser relevance to them.

The reasons for non-fulfillment and non-persistence were largely consistent across the five chronic diseases. Respondents with osteoporosis and hyperlipidaemia had the highest endorsement of medication concerns as reasons for non-fulfillment and non-persistence. Possible side effects of oral-bisphosphonate therapy (such as muscle, joint, and bone pain, and gastrointestional upset) and statin therapy (such as skeletal

muscle pain and tendon impairment) have received coverage in both the popular press, vis-a-vis direct-to-consumer advertisements, and on health and medical websites. Respondents with osteoporosis were more likely to cite regimen difficulties as a reason for non-persistence, which is consistent with the routine of having to take oral bisphosphonates before any food or liquid is ingested and remaining upright for 30–60 min. Compared to the other four study diseases, respondents with osteoporosis were more likely to endorse they did not think their condition was life threatening as a reason for non-fulfillment and non-persistence, which is consistent with literature documenting that that women perceive osteoporosis to be a less serious condition compared to other diseases[S60] and that women do not perceive themselves to be at risk for osteoporosis.[S60–S62]

We cross-validated most of the self-reported reasons for non-fulfillment and non-persistence against precise multi-item scales that measured matched constructs. With one exception (patient knowledge), these results supported the validity of self-attributed reasons. The multi-item scale assessing patient knowledge was unrelated to the reason associated with not understanding the purpose of the medication. Two factors may account for this finding: (i) only 3.4% of non-fulfillers and only 1.1% of the non-persisters cited this reason and (ii) significant ceiling effects (13%) and near-ceiling effects (23% scoring 90 and above) were observed on the knowledge scale. Both of these facts would serve to attenuate the results of the tests of convergent validity. We did not develop multi-item scales to assess regimen intrusiveness, forgetfulness, perceived drug efficacy and perceived drug benefit; thus, the convergent validity of those reasons remains unsubstantiated.

This study is not without limitations. Relative to the US adult population, our internet-based sample had a slight under-representation of adults with an income less than $25 000 annually,[S63] an under-representation of adults with less than a high school education, an over-representation of adults with a college education, and over-representation of Caucasians.[S64–S65] Further, some differences were observed between those who were successfully and non-successfully contacted for survey participation in terms of age, race and education. The literature provides little guidance as to whether the reasons for non-fulfillment and non-persistence might vary as a function of age, race, and education and whether different results might have been obtained with a more diverse sample. However, a rigorous meta-analysis[S66] reported age to be unrelated to adherence, and education was very weakly associated with adherence. It is plausible that the slight income bias would provide a *lower-bound* estimate on observed results for financial hardship as reasons for non-fulfillment and non-persistence.

Social desirability may also have influenced the frequency of reported reasons. It is plausible that respondents might find it more cognitively acceptable to attribute a clinical reason for stopping a medication (e.g. side effects) than to cite a reason that might be associated with personal limitations (e.g. did not understand the purpose of the medication). If social desirability bias was operating, it was highly consistent across the five studied diseases.

Only five chronic diseases were studied, and none of them were substantiated with medical records. However, a well-defined chronic disease panel was accessed and the five conditions were verified using a separate, independent screener than that used to enrol the Harris CIP. No psychiatric conditions were studied. Another study limitation is that sample specification was based solely on self-reported non-fulfillment and non-persistence – no external indicators of non-fulfillment or non-persistence, such as pharmacy claims, were available. However, past research has demonstrated that patients reliably report non-adherence.[S67]

We asked only 10 reasons for non-fulfillment and 12 reasons for non-persistence. It is possible that other salient reasons were omitted from the survey. Respondents were only asked to check all of the reasons that applied to them. They were not asked to rank order the relative importance of each checked reason. Future research should assess the relative importance of reasons for non-

fulfillment and non-persistence in addition to their mere presence or absence. We did not inquire about unintentional non-adherence (sporadic dose skipping), which has been documented to be prevalent among patients.[30,S68–S70] It is unknown whether and to what extent the reasons we studied for non-fulfillment and non-persistence might also apply to sporadic dose skipping.

Our observed results could have practical implications for the design and evaluation of future adherence interventions. Consistent with recommended standards,[S13] adherence interventionists should first conduct qualitative discovery research with target populations to understand their unique, patient-centred barriers toward adherence. Such qualitative research should investigate both perceptual barriers, as we found in this research, as well as practical barriers. Relatedly, future adherence interventions should specify *a priori* whether the content focus of the interventions(s) is on intentional non-adherence – where patients decide to eschew therapy based on their perceptual barriers to medications – or unintentional non-adherence – where patients face practical difficulties in following prescription medication therapy. Among the 2756 non-persisters surveyed in our study, only 12.2% of them cited forgetfulness as a reason for stopping their medication. Interventions that focus solely on reminder devices to improve unintentional non-adherence may need to be synergized with cutting-edge interventions related to medication concerns, perceived need for medications, and perceived medication affordability. Further, given the documented extent of non-fulfillment in both patient[3] and general populations,[3] it is timely and appropriate to design adherence interventions to not only improve persistence with therapy but also to increase medication fulfillment. However, such trials would have to be conducted within the context of an electronic prescribing system.

The therapeutic success of any medication is dependent on the fidelity with which patients adhere to the first-fill instruction and then dosing and refill instructions, and such fidelity is itself dependent on patient beliefs about their treatment and disease. A patient-centred approach to medication decision-making could allow for tailoring prescription-medication therapy to individual-patient needs for conditions for which there is more than one drug of the same or similar class that may differ in costs, side-effect profiles, or regimen intrusiveness. To achieve these goals, adherence interventions research needs to be conceptualized and implemented with a patient-centred focus that addresses perceptual barriers to non-adherence.

Conflicts of interest

Dr McHorney is a full-time employee of and owns stock in Merck & Co., Inc. Dr. Spain is a full-time employee of and owns stock in Merck & Co., Inc.

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Supporting information

Additional supporting information may be found in the online version of this article:

Figure S1. Flow of participants.

Table S1. Characteristics of respondents.

Table S2. Frequency of medication affordability, medication concerns, and lack of perceived need as reasons for medication non-fulfillment and non-persistence.

Table S3. Convergent validity related to prescription medication costs among non-fulfillers (N = 236) and non-persisters (N = 927).

Data S1. Supplemental references.

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