

Review Article

Primary Non-Adherence of Prescribed Pharmaceutical Treatments and Interventions: An Investigative Review to Improve Quality in Primary Care

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ABSTRACT

Aim: To review non-disease-specific predictors and causes of primary non-adherence of prescribed pharmaceutical treatments and interventions.

Method: A PubMed literature search (up to October 2015) using the terms primary, initial, first-fill and index with terms related to non-initiation, adherence, compliance, redemption and dispensing. The references, citations and similar articles for the identified articles were used to identify additional sources.

Study selection and data extraction: Prescription record-based and survey-based studies considering at least four medication classes or diseases while evaluating factors (predictors and causes) associated with primary non-adherence were examined.

Results: 53 articles were identified, including 16 specific to cost-related primary non-adherence. Regularly cited factors were age, gender, race and ethnicity, mental health, comorbidities, polypharmacy, medication beliefs, side effects, affordability, education, number of clinic, hospital and emergency department visits, patient-physician relationship, prescriber traits, forgetfulness and convenience. Issues related to affordability were raised most frequently, being brought up in 37of 53 sources. Many of the articles provided conflicting reports as to the direction of predictors and the importance of causes of primary non-adherence.

Conclusion: To date, numerous factors have been identified and associated with primary non-adherence to medications. Some factors may appear to be more influential than others, though the relevance of each predictor and cause varied between studies. To date, discrepant data in the literature has prevented the homogeneous analysis of primary adherence to prescribed pharmaceutical treatments. By compiling the factors and barriers related to primary non-adherence, this investigative review will prompt and promote future research in this area. Ultimately, primary care physicians will be better equipped to understand, act and potentially prevent patients from avoiding treatment regimes at the outset.

Keywords: Patient compliance; Medication adherence; Primary health care; Prescriptions; Therapeutics

How this paper fits in with quality in primary care?

What do we know?

The current literature highlights a multitude of factors which may play a role in primary adherence to prescribed pharmaceutical treatments and interventions in primary care. However, there is a paucity of original research investigating why patients do not adhere to primary pharmaceutical treatments and interventions. Furthermore, there is no standard approach to the study of primary non-adherence and there are no clear guidelines indicating how primary non-adherence should be defined. To date, discrepant data in the literature has prevented the homogeneous analysis of primary adherence in this capacity. This investigative review is the first step in informing future research to improve the quality of health outcomes related to primary adherence to medications in primary care.

What does this paper add?

There is a limited number of original research articles, and a complete absence of review articles that investigate the phenomenon of unfulfilled prescriptions in primary care. This comprehensive, investigative review is the first of its kind to compile the documented factors associated with primary non-adherence of prescribed pharmaceutical treatments and interventions in this

setting. During our investigation, we also discovered that some factors may appear to be more influential than others, though the relevance of each predictor and cause varies between studies. This paper fills a large gap in the extant literature. It increased our understanding of the factors associated with primary non-adherence in primary care, which in turn will ignite future research, and eventually lead to an increase in "fulfilled" treatment regimes. This will also result in better quality, not just for individuals, but for groups, communities and entire health care systems, in both the public and private sectors.

Introduction

Health care professionals and researchers are becoming increasingly aware of the challenges associated with the primary non-adherence of pharmaceuticals. Unlike secondary non-adherence, which includes improper dosing and a lack of persistence in medication taking, primary non-adherence concerns patients who fail to ever begin a prescription drug regimen. The terms "primary noncompliance", and "initial therapy defaulting" have also been used to refer to this phenomenon.

Primary non-adherence encompasses patients who never obtain their medications, as well as patients who fail to begin taking medications after picking them up from their pharmacist. As it is difficult to study the latter, primary non-adherence is frequently studied by strictly examining rates of prescription non-fulfillment by using prescribing records and pharmacy claims databases. Alternatively, primary non-adherence can be studied using data collected through patient surveys or by using a combination of self-reported and electronically-recorded data. But why is the overall study of primary non-adherence important? Other than the obvious reasons that avoiding prescribed pharmaceutical treatments and interventions can and in many cases, will lead to adverse health effects; it is also necessary to get a better sense of the extent of this problem so that improvements in the quality of our health care delivery systems can begin. This study is not a systematic review; rather, it was designed as an investigative review that is necessary to inform and sprout further research in this area.

We will begin our investigation by examining the current literature relating to primary non-adherence among general populations.

Initially, we examined studies that explored both single and multiple drug classes associated with diseases and conditions linked to initial medication adherence. Other general factors include: identified patient characteristics, prescription cost, comorbidities and medication class [1].

Specific diseases including: asthma [2-4], hypertension [5-8], diabetes [9-11] and osteoporosis [12-14] have been the subjects of multiple studies on primary non-adherence; however, primary non-adherence has not been well-studied among individuals with less common afflictions. Given these inconsistencies in the literature, we sought to understand the factors that underlie medication fulfillment, regardless of population, disease and medication-specific factors.

Methods

Data sources and selection criteria

A keyword search in PubMed from inception until October 2015 was conducted using the terms listed in Table 1. Specifically, search terms used were based on 4 core concepts using a controlled vocabulary of keywords related to the following terms: 1) primary, 2) adheren*, 3) complian*, and 4) redemption in a health care setting. The investigation also used the opposite terms (e.g. non-adherence, noncompliance and non-redemption). Further studies were identified among the references and citing articles of key resources. For all sources indexed in PubMed, the listings of "similar articles" were also searched. Identified studies were evaluated and relevant findings were reported. The search and review criteria were developed by the authors, who include a medical librarian with extensive experience conducting comprehensive literature reviews. Articles meeting criteria were reviewed by the first author, and consensus for inclusion was reached through subsequent discussions with the other 2 authors.

The first inclusion criteria was that studies must classify individuals as either primary adherent or non-adherent using records, such as pharmacy claims databases, or self-reports. To be included, the studies were also required to identify either predictors or reasons for medication non-fulfillment. Studies identifying predictors relied on statistical analyses comparing adherent and non-adherent cohorts in order to identify relevant univariate and multivariate predictors associated with medication non-fulfillment. In contrast, studies aiming to establish causes for primary non-adherence relied on interviews and surveys of patients identified as non-fulfillers. Several included studies used both approaches to determine both predictors and causes.

A subset of survey-based studies examining cost-related primary non-adherence were also included as they met the above selection criteria.

In order to negate the confounding effects of particular disease-related factors on medication redemption, articles specific to a limited number of diseases or drug classes (3 or less) were excluded.

Due to the likelihood that adherence behaviour among paediatric patients is distinct from that of the general population because medication fulfillment is typically controlled by a parent or guardian; articles looking uniquely at patients under the age of 18 were excluded. While adherence is likely even more critical for patients discharged from the emergency department or hospital, articles specifically examining such patients were

Table 1: Search terms for identifying articles on primary non-adherence.

primary	non-adheren*	non-complian*	redemption
initial	non-adherence	non-compliance	non-redemption
first-fill	adherence	compliance	non-dispens*
index	non-initiation		

excluded because it was felt that these individuals would not be reflective of the general population in terms of medication fulfillment. It should be noted, however, that these patient groups were present in many of the larger studies on primary non-adherence, but only consisted a minority of the samples.

Articles were also excluded if they were not available in English or if they studied medication non-fulfillment, but then made no distinction between primary and secondary non-adherence in the analysis. Finally, qualitative articles lacking data to support the validity of a predictor or cause of primary non-adherence were excluded.

Results

A total of 53 eligible articles were identified. Data was extracted my one author with a 20% check of a second reviewer to confirm inter-rater reliability. Of the articles that considered non-cost-related primary non-adherence, 15 relied solely on prescribing records, 9 only used surveys and 13 employed both approaches (Table 2). The 16 articles specific to cost-related non-adherence were all survey based (Table 3).

The articles that were not specific to cost estimated that

Table 2: Studies on primary non-adherence.

Prescribing records

Study	Country	Sample size	Sample source	Design	Time allowed for prescription fulfillment	Primary non-adherence rate	Factors
Beardon et al. [38]	Scotland	4,854 (20,921[a])	Single health centre	Analysis of prescription copies	4-7 months	14.5% (5.2%[a])	Age, gender, affordability, prescriber, other (weekend)
Begg [65]	Scotland	1,395[a]	Single practice	Analysis of prescription copies	6 months	6.4%	Affordability
Ekedahl et al. [18]	Sweden	317	Large community pharmacies in two northern counties	Intervention study (mail and telephone reminders) with analysis of electronic records	3 weeks	-[b]	Age, gender, forgetfulness
Fischer et al. [35]	U.S.	195,930[a]	1,217 prescribers who began e-prescribing in Massachusetts	Analysis of electronic records	0-12 months	22.5%[a]	Age, gender, prescriber, other (practice size)
Fischer et al. [36]	U.S.	423,615[a]	Single pharmacy benefit management company	Analysis of electronic records	6 months	24.0%[a]	Age, gender, affordability, prescriber
Gardner et al. [21]	New Zealand	49,756[a]	13 practices	Analysis of electronic records	Not specified	9.8% (13.0%[a])	Age, gender, affordability
Hagstrom et al. [43]	Sweden	399	Single primary health centre	Intervention study (telephone reminders) with analysis of prescription copies	5 weeks	9.3% (intervention: 5.5%; control: 12.6%)	Gender, forgetfulness
Jackson et al. [45]	U.S.	29,238[a]	100 pharmacies in the mid-south	Analysis of electronic records	30 days	12.2%[a]	Gender, polypharmacy, affordability, prescriber, other (pharmacy dispensing volume)

Linnet et al. [64]	Iceland	21,571	Primary health centres in and nearby Reykjavik	Analysis of electronic records	3 months	6.2%	Affordability
Loong [26]	Singapore	500	Single physician	Matching of physician and pharmacy records	Not specified	4.0%[a]	Age, gender, affordability, other (acute/chronic)
Pottegard et al. [27]	Denmark	307,678[a]	83 GPs	Analysis of electronic records	4 months	9.3%[a]	Age, gender, comorbidities, polypharmacy, affordability, education, prescriber
Shin et al. [41]	U.S.	569,095[a]	Large managed care organization in southern California	Analysis of electronic records	14 days	9.8%[a]	Age, gender, race, mental health, comorbidities, polypharmacy, affordability, clinic/hospital/ED visits, prescriber, others (brand/generic, acute/chronic, symptoms, weekend)
Shrank et al. [28]	U.S.	10,349,139[a]	Prescriptions filled at a large retail pharmacy chain by members of a single pharmacy benefits manager	Analysis of electronic records	30 days	3.27%[a,c]	Age, gender, polypharmacy, affordability, other (brand)
Tamblyn et al. [16]	Canada	37,506[a]	131 physicians in a primary care research network	Analysis of electronic records	9 months	31.3%[a]	Age, gender, comorbidities, polypharmacy, affordability, clinic/hospital/ED visits, P-P relationship, prescriber
Waters et al. [44]	England	2,393[a]	Single general practice	Matching of duplicate prescriptions	Not specified	6.1%[a]	Gender, prescriber
Surveys							
Study	**Country**	**Sample size**	**Sample source**	**Design**	**Recall period**	**Primary nonadherence rate**	**Factors**
Arslan et al. [17]	Turkey	280	Single health centre	In-person surveys	5 days	8.6%	Age, gender, affordability, other (negligence)
Craig et al. [53]	U.S.	74,949	Non-institutionalized senior Medicare beneficiaries	Computer-assisted personal surveys	9-12 months	2.39%	Side effects, medication beliefs, affordability, convenience, other (don't like taking)

Johnell et al. [23]	Sweden	15,865	Random sample from 6 central regions, specifically including respondents with an ED, hospital or PCP visit in the last three months.	Mail surveys	3 months	7.1%	Age, comorbidities, medication beliefs, affordability, education
Kerse et al. [66]	New Zealand	172	14 GPs in 22 practices	In-person surveys with telephone follow-up	4 days	21.4%	P-P relationship
McHorney and Spain [55]	U.S.	7,365	National chronic-illness panel members who received at new prescription in the last year	Internet surveys	12 months	4.0%	Side effects, medication beliefs, affordability, convenience
Thunander Sundbom and Bingefors [30]	Sweden	2,802	Cross-sectional, random, national sample of people aged 18-84 years	Mail surveys	Not specified	-[e]	Age, gender, comorbidities, medication beliefs, affordability, education
Thunander Sundbom and Bingefors [49]	Sweden	2,802	Cross-sectional, random, national sample of people aged 18-84 years	Mail surveys	Not specified	-[e]	Mental health
Wamala et al. [59]	Sweden	31,895	National sample	Mail surveys	3 months	6.5%	Medication beliefs, affordability, education
Wroth and Pathman [32]	U.S.	3,926	Sample from rural areas in 8 south-eastern states	Telephone surveys	12 months	21.6%	Age, gender, race, comorbidities, affordability, education, P-P relationship, convenience, others (marital, clinic staff)

Combination

Study	Country	Sample size		Sample source	Design	Time allowed for prescription fulfillment	Primary non-adherence rate	Factors
		Total	Non-adherent survey					
Ax and Ekedahl [42]	Sweden	44,607[a]	340	Single county	Analysis of electronic records followed by mail surveys	3 months	2.5%[a]	Gender, medication beliefs, affordability, forgetfulness
Ekedahl and Mansson [34]	Sweden	89,533[a]	87	3 southern health care districts	Analysis of electronic records followed by telephone surveys	4-7 months	2.37%[a]	Age, gender, medication beliefs, affordability, forgetfulness

Esposito et al. [19]	U.S.	1,214	172	6 military pharmacies	Telephone surveys and analysis of electronic records	12 months[f]	Self-report: 8.8% Prescription data: 40.6%	Age, gender, comorbidities, medication beliefs, education, forgetfulness, convenience, other (pharmacy staff)
Fincham and Wertheimer [58]	U.S.	10,695[a,g]	87 (control: 188)	A HMO of a large midwestern city	Analysis of abandoned prescriptions followed by mail surveys	2 weeks	3.02%[a]	Medication beliefs
Fischer et al. [20]	U.S.	4,822	50	Family and internal medicine departments in a single-state health system	Analysis of electronic records followed by telephone interventions and surveys	30 days	6.0%	Age, medication beliefs, affordability, forgetfulness
Hakim [54]	U.S.	17,625[a]	93	233 private practice clinicians	Analysis of electronic records followed by surveys	Not specified	15.0%[a]	Side effects, medication beliefs, affordability, forgetfulness, other (cost information, symptoms)
Jones and Britten [62]	England	935	18	Single practice	Mail survey followed by in-person surveys	Not specified	2.9%	Affordability
Kennedy et al. [25]	U.S.	14,464	664	Non-institutionalized, elderly and nonelderly Medicare beneficiaries	Computer-assisted personal surveys	9-12 months[f]	4.6%	Age, gender, race, mental health, comorbidities, side effects, medication beliefs, affordability, convenience, other (don't like taking)
Kinnaird et al. [68]	Italy	28,000[a,h]	124	Active and retired U.S. military personnel and their families	Analysis of electronic records followed by telephone surveys	7 days	2.8%[a]	Forgetfulness, other (chose not to)
Leu and Eng [67]	Thailand	93,919[a,g]	91	Outpatient pharmacy at a tertiary hospital	Analysis of electronic records followed by a mail surveys	7 days	0.74%[a]	P-P relationship, forgetfulness, convenience
Papke [56]	U.S.	18,233[a]	263	Main outpatient pharmacy of an army community hospital	Analysis of electronic records followed by telephone surveys	5 days	4.7%[a]	Side effects, medication beliefs, forgetfulness, convenience

Sherratt et al. [15]	England	165,155[a]	10	Twenty general practices in the Gateshead Primary Care Trust	Identification of uncollected prescriptions and analysis of electronic records followed by in-person interviews	4 weeks (and which was not expected to be collected)	0.5%[a]	Forgetfulness, other (specific diagnosis vs. symptom relief vs. presumptive diagnosis)
Stuart [57]	England	986[a]	65	Single practice	Matching of duplicate prescriptions followed by mail surveys	Not specified	7.6%[a]	Medication beliefs, affordability, prescriber

[a] Value represents total prescriptions rather than total patients
[b] The initial sample only included individuals who had not claimed e-prescriptions after 4 days
[c] 1.50% of the total prescriptions were abandoned by patients who obtained another prescription for a drug in the same class
[d] Studies based on the same data
[e] 66.4% reported some form of non-adherence including: forgetting to take medication; filling a prescription, but not taken any medication; changing dosage without medical consultation; discontinuing treatment; not filling a prescription. Rates were not provided for separate non-adherent behaviours, but some analyses were specific to behaviours
[f] Recall period used for a patient survey rather than time allowed for prescription fulfillment
[g] Total number not specified. Calculated based on available data
[h] Total number not specified. Approximate number provided

Table 3: Studies specific to cost-related primary non-adherence.

Study	Country	Sample size	Sample source	Design	Recall period	Primary non-adherence rate	Factors
Afulani et al. [37]	U.S.	10,401	National survey panel; using data specific for non-institutionalized seniors	In-person and telephone surveys	12 months	4.7%	Age[a], gender, race, mental health, comorbidities, affordability, education, other (marital, family, smoking, alcohol)
Donelan et al. [61]	Australia, Canada, New Zealand, U.K. & U.S.	4,058	Non-institutionalized adults	Telephone and in-person surveys	12 months	14%	Affordability[b]
Frankenfield et al. [46]	U.S.	272,701	Non-institionalized Medicare beneficiaries	Mail and telephone surveys	6 months	13.4%	Race
Gellad et al. [47]	U.S.	14,829	Medicare beneficiaries	Mail and telephone surveys	12 months	19.0%	Race
Herman et al. [39]	U.S.	44,574	National survey panel; using data specific for non-institutionalized respondents aged 18-64	In-person and telephone surveys	12 months	11.2%	Age[a], gender, race, mental health, comorbidities, affordability, education, other (marital, family, smoking, alcohol)
Jatrana et al. [22]	New Zealand	18,320/ 17,035[d]	National survey panel	In-person surveys	12 months	6.4%	Age, gender, race, mental health, comorbidities, affordability, education, P-P relationship, Other (marital, family, smoking)

Kennedy and Erb [48]	U.S.	25,805	Non-institutionalized individuals with impairments, functional limitations, chronic conditions or receipt of disability benefits	In-person surveys	Not specified	19.5%	Race
Kennedy et al. [40]	U.S.	43,568	National sample	In-person surveys	12 months	6.2%	Age, gender, race, comorbidities, affordability, clinic/hospital/ED visits
Kennedy and Morgan [24]	U.S. & Canada	8,688	National sample	Telephone surveys	12 months	9.4%	Age, gender, race, comorbidities, affordability
Neuman et al. [63]	U.S.	16,072	Non-institutionalized. senior Medicare beneficiaries	Mail and telephone surveys	12 months	15.6%	Affordability
Safran et al. [50]	U.S.	10,416	Non-institutionalized seniors in 8 states	Mail and telephone surveys	12 months	22%	Comorbidities, affordability
Safran et al. [52]	U.S.	17,569	Non-institutionalized senior Medicare beneficiaries	Mail and telephone surveys	12 months	18.3%	Polypharmacy, medication beliefs, affordability
Simon-Tuval et al. [29]	Israel	522/514[e]	Enrollees in Israel's 2nd largest health plan aged 55 and older who were part of the Diabetes and Cardiovascular Disease Registry	Telephone surveys	12 months	9.6%	Age, gender, medication beliefs, affordability, education
Wagner et al. [31]	U.S.	2,869 (8,543)[f]	National sample of Americans 50 and older	Telephone surveys	12 months[g]	-[h]	Age, gender, race, mental health, comorbidities, polypharmacy, affordability, education, other (marital)
Wilson et al. [51]	U.S.	17,569	Non-institutionalized senior Medicare beneficiaries with over sampling of Medicaid enrollees and seniors in low-income neighborhoods	Mail and telephone surveys	12 months	18.3%	Comorbidities
Zivin et al. [33]	U.S.	3,071	Nationally representative sample of Americans aged 65 and older who were able to be self-respondents	In-person survey for the Health and Retirement Study (HRS) followed by a mail survey for the HRS Prescription Drug Study	12 months	-[h]	Age, gender, mental health, comorbidities, side effects, affordability

[a] Studies based on the same survey. Afulani et al. [37] considered ≥ 65 years, Herman et al considered <65 years. Considered concurrently, the studies suggest a U-shaped relationship with non-fulfillment being most common for those in the mid-range of ages

[b] Analysis looking at affordability (insurance coverage) was specific for Americans

[c] Studies using the same data. Gellad et al. [47] excluded 2,037 individuals who had not taken at least one prescription in the last year, 615 individuals with races other than "White", "Black" and "Hispanic" and 93 individuals with no recorded race or ethnicity. For results unrelated to race, the data from the larger sample used by Safran et al. [50,52] was referred to

[d] Not all patients had complete data for the regression analyses

[e] Not all patients were included in the statistical analyses

[f] There were 2,869 survey respondents, but the analyses examined the 8,453 prescriptions reported by the survey respondents

[g] A separate analysis of respondents who reported not filling prescriptions at least once a month was not considered in this review

[h] The study does not indicate what percentage of respondents reported not filling new prescriptions due to cost

anywhere from 0.5% [15] to 31.3% [16] of all prescriptions are never redeemed.

Our investigative review of the literature yielded a total of 15 factors associated with primary non-adherence. The factors most commonly cited included: 1) age, 2) gender, 3) race and ethnicity, 4) mental health, 5) comorbidities, 6) polypharmacy, 7) side effects, 8) medication beliefs, 9) affordability, 10) education, 11) number of visits to the clinic, hospital or emergency department, 12) patient-physician relationship, 13) prescriber characteristics, 14) forgetfulness, 15) convenience, and 16) other factors, such as brand-name vs. generic prescription options.

Age

Many studies suggest that the rate of primary non-adherence decreases with age [16-33], though some studies have found that prescription fulfillment becomes worse again among the elderly [34-36]. Alternatively, some studies have identified a U-shaped relationship whereby non-adherence is highest among individuals in the mid-range of ages [37-40]. Shin and colleagues identified this sort of relationship for chronic medications (defined as all medications, except for anti-infective, analgesics and migraine medications), but found that primary non-adherence was the lowest for individuals aged 21-50 when acute medications were studied [41] (Figure 1).

Gender

Inconsistent results have also been obtained when gender has been studied. While many studies [25,28,32,35,36,38] including studies on cost-related primary non-adherence [22,31,33,39,40] have discovered adherence to be lower among women, the opposite result has also been obtained [29,34,42-44]. As with age, Shin et al. found opposite relationships depending on treatment type: men were less likely to fill medications for acute treatments, but were more likely to obtain medications for chronic treatments [41]. Thunander Sundbom and Bingefors also obtained discrepant results, finding that women were more likely to not start filled prescriptions, but also finding that neither gender was more likely to not fill prescriptions [30]. Many other studies have determined that patient gender is not associated with primary adherence [16-19,21,24,26,27,37,45] (Figure 2).

Race and ethnicity

Studies carried out in the U.S. have focused on comparing individuals classified as "White", "African American" and "Hispanic" because the under-representation of other races and ethnicities prevents meaningful statistical analysis. American studies typically identify higher rates of both cost-related and non-cost-related initial non-adherence among patients identified as Hispanic or African American [25,32,37,40,41,46-48] There are exceptions, however, such as two cost-specific studies which found race to be inconsequential, [24,31] and another study which associated Asian ethnicity with cost-related non-adherence, but found no difference between other groups [39].

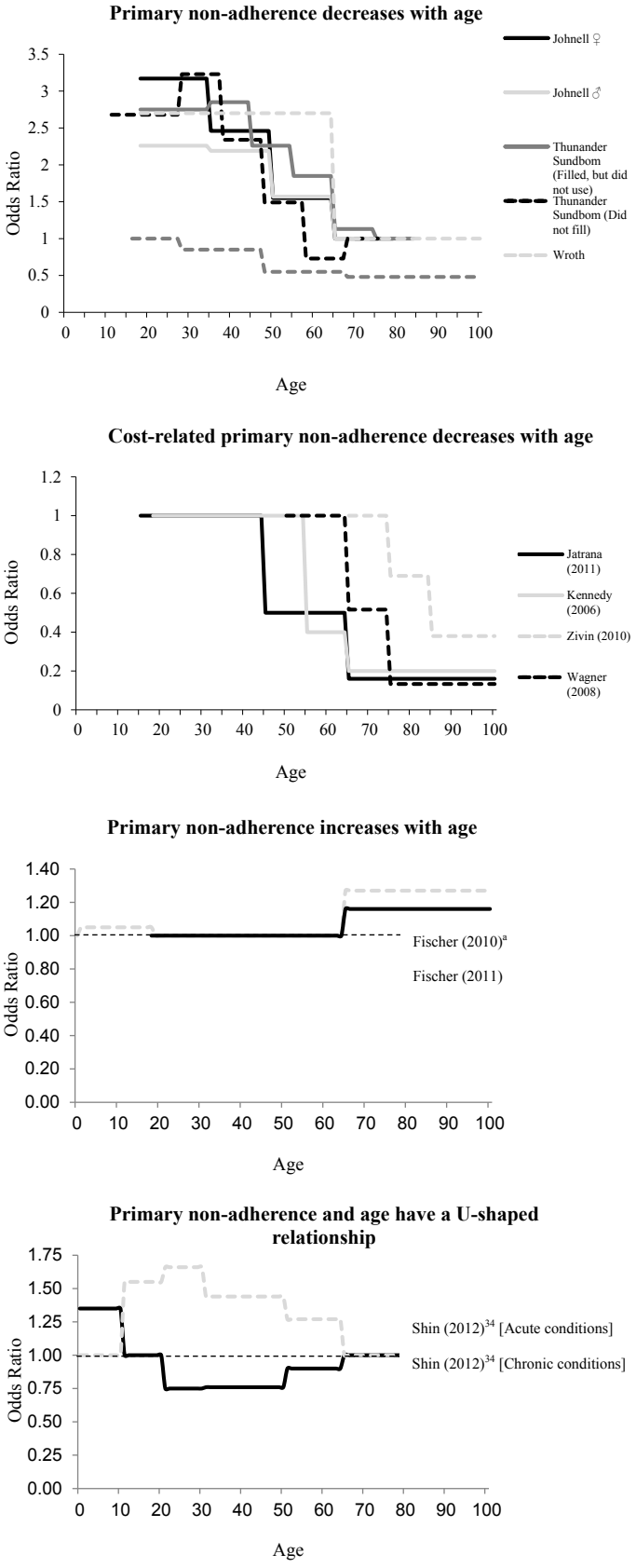
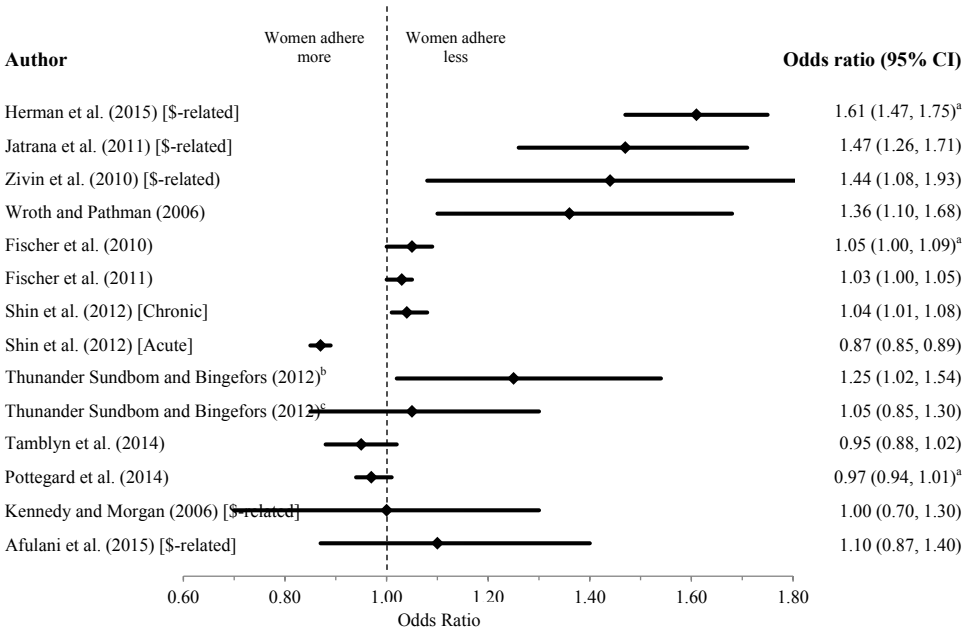


Figure 1: Odds of primary non-adherence in function of age. Odds ratios that were not statistically significant were considered to be equal to 1.

[a]Original source presented odds ratios for primary adherence; odds ratios calculated for primary non-adherence



[a]Original source used females as the referent group; odds ratio calculated for males as the referent

[b]Data for patients who filled a prescription, but did not start taking the medication

[c]Data for patients who did not fill a prescription

Figure 2: Forest plot of odds ratios for primary non-adherence by women compared to men. The diamond represents the odds ratio; the lines represent the 95% confidence intervals [16,22,24,27,30,32,33,35-37,39,41].

One study from New Zealand also identified significant variability between ethnic groups in finding that compared to individuals classified as "NZ/European", cost-related prescription nonfulfillment was reported by individuals identified as "Maori" and as "Pacific" 1.31 and 2.17 times more often, respectively [22].

Mental health

The importance of patients' mental health in regards to prescription non-fulfillment has not been examined extensively. It has been found, however, that dementia, depression and anxiety can be linked to increased odds of initial non-adherence [41,49]. A separate study found that Medicare beneficiaries with psychiatric conditions were more likely to report primary non-adherence [25]. Additional studies, which have associated cost-related non-adherence with various aspects of mental health [22,31,33,37,39], would seem to support these findings

Comorbidities

Studies, including several specific to cost, have found that the rate of initial noncompliance is higher among patients with chronic conditions (particularly if they have a multiple comorbidities) and with a lower health status [16,22-25,30-32,37,39,40,50,51]. In contrast, the relationships between specific health conditions and primary non-adherence are inconsistent. While some diseases, such as cancer and renal disease, have actually been associated with decreased odds of prescription non-fulfillment [41] other conditions, such as arthritis and lung diseases, have had opposite relationships with adherence in different studies [19,25,27,33,41].

Polypharmacy

Conflictingly, some researchers have found that individuals on more drugs are significantly more likely to not fill prescriptions [27,28], while others have found the opposite [16]. Shin et al. even suggested that individuals on more drugs are more likely to obtain drugs for chronic treatments, but less likely to obtain medications for acute treatments [41].

With the exception of a study which found no relationship between polypharmacy and cost-related primary non-adherence [31], most evidence would point to polypharmacy as a predictor of primary non-adherence. For example, two studies found that patients receiving multiple prescriptions on the date of the index prescription were more likely to be non-adherent [41,45] and a survey-based study found that nearly 1 in 10 senior, non-institutionalized Medicare beneficiaries did not acquire new prescriptions as they were already on an immoderate number of medications [50].

Side effects

Like polypharmacy, the possibility of adverse events can make a drug regimen seem like more of a burden and prevent therapy initiation. In fact, surveys of non-adherent individuals have found that up to 47% of medication nonfulfillment can be attributed to the fear of side effects and drug interactions [25,52-56]. According to one study, individuals who have experienced adverse drug events are more than two times more likely to report cost-related primary non-adherence [33]. Concerns about side effects may be related to the finding that individuals who are treatment naïve tend to be less likely to fill their prescriptions [28,35,36,41], since individuals who have previous experience with a drug are less likely to consider themselves to be susceptible to adverse events.

Medication beliefs

In studies evaluating the impact of patient's beliefs about the medications prescribed to them, the perceptions that medications will not work or that they are not necessary accounted for up to 45% of primary non-adherence [19,20,25,34,42,52-57]. More drastic beliefs, such as the perception of medications as "dangerous" or as a "necessary evil", have also been associated with primary non-adherence [30]. Such negative medication beliefs may be related to the low levels of trust in the health care system commonly reported among initially non-adherent patients [23,58,59]. Alternatively, the lack of belief in the efficacy and importance of prescriptions may be related to the findings that many non-adherent patients report uncertainty or dissatisfaction in regards to the directions provided [54,55] and that rates of nonfulfillment are greater among individuals who report not having received directions for using their prescriptions [19,29,58].

These findings are supported by a unique study comparing totally adherent individuals to those who were persistent with the exception of one unfilled medication. This study found that completely adherent individuals had a higher perceived need for medications and a greater level of knowledge about their prescriptions [60].

Affordability

In 1999 a group of researchers asked approximately 1,000 individuals from each of 5 different nations whether they or a family member had ever not filled a prescription due to cost. Significantly, cost-related primary non-adherence was reported by 6% to 17% of individuals, with Americans being the most likely to acknowledge this issue [61].

When patients identified as primarily non-adherent are interviewed, anywhere from 5% to over 50% of patients report cost to have been a key factor in the decision to not redeem a prescription [17,20,25,26,34,42,53-55,57,62]. It is therefore, unsurprising that many socioeconomic factors, which presumably play a role in drug affordability, have been linked to prescription nonfulfillment. These include food insecurity [39,37], financial strain [23], poor financial status [17], low net worth [33], economic problems [30] and severe socioeconomic disadvantage [59]. Unemployment may also predict primary non-adherence [29,32,39], except among the elderly, for whom employment may be a sign of financial instability [37].

Moreover, with the exception of two studies, which did not find patient income to be significant [31,41] increasing patient income level has unanimously been associated with decreased odds of primary non-adherence, including cost-related non-adherence [22,24,25,27-29,32,36,37,39,40,50,52,63].

Despite this evidence, high income cannot be relied upon as a predictor of medication fulfillment. When Gardner et al. considered government subsidy provided for medications (therefore indirectly studying income level), they discovered that patients who had to pay the full cost of their medications due to their high incomes had higher rates of primary non-adherence [21]. Consequently, it would seem that high income individuals are more likely to adhere only when compared to low income patients facing identical copayments.

With the exception of a single Icelandic study, which found that minor increases in copayments (€1 to €3) did not have a significant effect [64], higher out of-pocket costs have been consistently associated with increased odds of nonfulfillment [16,28,31,33,38,45,65]. Correspondingly, three studies allowing patients to report reasons for medication nonfulfillment found that health insurance, a factor which influences copayment level, was a key contributor to non-adherence for 12% to 20% of respondents [25,53,55]. Additional studies examining cost-related primary non-adherence have supported the link between health insurance and adherence [24,33,37,39,50,52,61,63]. In Israel, however, where universal health coverage is provided to every citizen, supplemental insurance has no impact on the rate of cost-related primary non-adherence [29].

Education

The majority of studies examining patient education level have not identified a link to initial medication adherence [22,23,27,29,31,32,37,59], though there are exceptions. Two studies found that primary non-adherence was more common with increasing education level [30,39] and another study, which was specific to the U.S. Military Health System, found education level to be mainly insignificant, but did show that primary non-adherence is less common for individuals with more than a 4-year college degree [19].

Clinic, hospital and emergency department visits

Rates of primary non-adherence have been found to be both higher and lower for patients who have had hospitalisations or emergency department visits with the past 6 or 12 months [16,40,41], thus the importance of a patient's recent hospital experience remains unclear. Similarly, the influence of the frequency of a patient's physician visits cannot be determined as this factor has only been evaluated in one study, which found that cost-related non-adherence was more commonly reported among patients who had 10 or more physician visits in the previous year [40].

Patient-physician relationship

An American study found that individuals with a regular source of care were 6 times more likely to be adherent compared to individuals who did not attend a regular clinic or consistently see the same physician [66]. This finding was supported by a Canadian study which discovered that prescription drug fulfillment was lower for patients who had fewer than 40% of their total clinic visits with the prescriber of the index prescription [16]. In contrast, a study carried out in New Zealand found that cost-related primary non-adherence occurs twice as often among patients who reported being affiliated with a primary care provider. Crucially, the authors of this study noted that patients who have a consistent relationship with a provider may have more opportunities to receive prescriptions, leading to higher drug costs and a greater likelihood of cost-related non-adherence [22]. An additional study disputes all of these findings by suggesting that the stability of a patient's source of

care has no influence on self-reported prescription delay and nonfulfillment [32].

Even if a patient regularly sees a physician, he or she is much less likely to be adherent if there is not a certain level of agreement and understanding between the patient and the physician. Consequently, patients tend to be less adherent if they do not trust, respect or have confidence in their prescriber [32,66,67].

Prescriber characteristics

Studies examining prescriber age [27,35,36,41] and gender [16,35,36,41] in relation to initial adherence have obtained inconsistent results as have studies looking at the prescriber's number of years of experience. The latter was found to be insignificant in some of studies [16,36] while others suggest that less experienced physicians have less adherent patients [38,41,44].

The single study exploring the role of prescriber race and ethnicity only found minor differences between different groups of physicians, but did discover that primary non-adherence was more common among patients who visited a prescriber of the same race or ethnicity as themselves [41].

Other factors such as physician specialty and prescribing volume have received limited analysis to date. While two studies found that specialists have higher rates of primary non-adherence compared to internists [35,36], other studies examined different specialties, preventing any meaningful comparison [41,45]. Similarly, prescribing volume has not been consistently defined, though two of the three studies considering prescription volume have suggested that high prescribers have more adherent patients [36,38,57].

Forgetfulness

Among studies identifying forgetfulness as a cause of primary non-adherence, anywhere from 2.2% to 19% of respondents reported not remembering to fill a prescription [15,19,20,34,42,54,56,67,68]. It should be noted, however, that patients may be more willing to claim that they did not remember to pick-up a medication than to admit that they did not trust or accept their physician's prescription. Some studies have supported this idea by showing that interventions to reduce forgetfulness, such as mail and telephone reminders, have limited effect on prescription fulfillment [18,20,43].

Convenience

Patient reports commonly show that inconvenience is an important barrier to prescription fulfillment with issues such overly long pharmacy wait times, being too busy and lacking time being cited frequently [19,25,56,67]. It has also been found that patients who report that getting to their physician's office is a challenge are more likely to report primary non-adherence, likely because their transportation challenges extended to the pharmacy as well [32]. To the same effect, Esposito et al. found that adherent patients were significantly more likely to consider their pharmacy's convenience, availability of parking and wait times as "excellent" [19].

An additional consideration is that a complex, and therefore inconvenient, drug regimen can be a cause for non-fulfillment [55].

Convenience-related barriers may only play a minor role in provoking primary non-adherence as they are never cited by more than 15% of non-fulfillers. For example, one study found that four convenience-related reasons ("didn't have time", "couldn't get the medicine soon enough", "no pharmacy convenient" and "didn't have a way to get medicine") collectively accounted for only 1.96% of primary non-adherence while cost was mentioned by one-third of non-adherent respondents [53].

Other factors

One survey found that 7.5% of non-compliant individuals did not obtain their medications because they had not been informed of cheaper options [54]. The cheaper options may have entailed over-the-counter products or generic medications, which are significantly less expensive than brand name drugs [69,70]. Consequently, this finding may relate to the evidence that patients appear to be less likely to obtain brand name drugs compared to generic alternatives [28,41].

The rate of primary non-adherence also appears to depend upon whether the treatment is for an acute condition or a chronic condition. For many of the previously described determinants, the distinction between acute and chronic treatments was demonstrated by the differing trends identified by Shin and colleagues [41]. The only other study which considered this potential difference found primary non-adherence to be more common for acute complaints [26].

A related issue explored by Shin et al. is that of the potential correlation between symptoms and adherence. In addition to demonstrating that prescriptions for asymptomatic diseases were less likely to be filled, the study found that medications for symptomatic, chronic conditions were almost 2 times more likely to be filled compared to those for asymptomatic, chronic conditions [41]. It is therefore unsurprising that one study found that the absence of symptoms was a factor contributing to primary non-adherence for one third of patients [54].

On a similar note, one study ranking drugs according to the Belfast Classification found that drugs that were frequently given for specific and certain diagnoses were the most likely to be filled, drugs given solely for symptomatic relief were second most likely to be filled and drugs that were frequently given for presumptive diagnoses were least likely to be filled [15].

A further factor investigated by Shin et al. was the day of the week on which the prescription was provided. More specifically, it was found that prescriptions given on weekends were less likely to be filled if they were for chronic conditions, but more likely to be filled if they were for acute conditions [41]. The only other study examining the day of the week did not differentiate between chronic and acute diseases, but did find that prescriptions given on the weekend were more likely to be abandoned [38].

Other factors which may warrant further investigation

include patient marital/family status and alcohol/tobacco use [22,31,32,37,39], practice size [35], pharmacy dispensing volume [45] and patient satisfaction with staff in the clinic [32] or pharmacy [19].

Finally, a few studies identified ambiguous causes for prescription nonfulfillment. In one of these, nearly one-third of respondents classified the motivation for their non-adherence as "negligence", without further explanation [17]. In another study, 29% of patients reported not filling their prescriptions because they did not want to [68]. Similarly, two studies found that 6.8% and 6.7% of patients, respectively, did not adhere because they "don't like taking medicine" [25,53]. All of these reasons are limited as it remains unclear if patients are opposed to therapy because they find medicine taking inconvenient or if another issue, such as the possibility of side effects, is responsible for this aversion.

Discussion

The current literature reveals and highlights a multitude of factors which may play a role in primary adherence. Many of the identified factors, including mental health, side effects, medication beliefs, patient-provider relationships and affordability, have also been associated with secondary non-adherence. In contrast, other factors related to secondary non-adherence, such as poor understanding of illness, insufficient follow-up and missed appointments, were not identified in this review [71].

Unfortunately, the studies included in this review are inconsistent in terms of which factors were investigated. This lack of standardization precluded our ability to include homogeneity in our analysis. The clear exception to this would be determinants related to affordability, which were considered in 37 of 53 studies. With the exception of 3 studies, which found either income or copayment to be inconsequential, all of these studies suggested that affordability plays a key role in adherence behaviour.

Two other factors which were explored relatively frequently included patient age and patient gender. Younger patient age was a reasonably strong predictor of primary non-adherence, but the fact that 8 out of 26 studies contradicted this relationship clearly weakens the evidence. Findings regarding gender were even more inconsistent, with 10 of 28 studies finding gender to be insignificant.

Among the studies evaluating causes of primary non-adherence, cost, concerns regarding side effects, low expectations of drug efficacy and forgetfulness all emerged as potentially significant reasons for prescription abandonment.

While the evidence is mixed for most of the other factors outlined in this review, it is important to acknowledge that most have not been evaluated to the point that any well-reasoned conclusion regarding their significance may be reached.

There are many limitations to this review, with the most significant being the lack of a standard approach for the study of primary non-adherence. The decision to adopt a non-systematic approach was motivated by this lack in the research literature. In brief, there is no consensus as to whether a survey-based or a prescription-record based approach is most appropriate since both have significant and distinct limitations. In the case of survey-based studies, this most notably includes recall bias, social desirability bias and non-response bias. Record-based studies, on the other hand, are susceptible to the incorrect classification of patients as non-adherent as a consequence of issues such as duplicate prescriptions and prescriptions which should have been cancelled due to a change in therapy. There also is no clear guideline as to how primary non-adherence should be defined, particularly in terms of how long a prescription can remain unfilled before a patient is considered initially non-adherent. While the failure to exclude articles on the basis of poor quality may weaken the findings of this review, a comprehensive listing of factors contributing to primary non-adherence was created and that potentially important factors that were evaluated in a limited number of articles, have not been ignored. This listing is the first of its kind, and will contribute to the growing body of evidence-based research on this topic.

The review is also limited by the inclusion of supplementary studies specifically evaluating cost-related primary non-adherence, which may partially explain the importance attributed to affordability. Finances are an important issue regardless and affordability was cited in 25 of the 37 studies that were not specific to cost. The cost-specific articles may also be problematic in that they classify patients who did not fill prescriptions for reasons other than cost as adherent. Despite this limitation, the studies specific to cost-related primary non-adherence generally supported the findings of the other sources.

Another limitation is the inclusion of studies from nations as varied as Scotland [38,65] Denmark [27], New Zealand [21] and Turkey [17]. While this gives a broad, universal perspective of adherence behaviour, country-based biases must be considered. An obvious example, which was demonstrated by the sole study conducted in Israel, is that affordability is a less important issue in countries where more extensive drug coverage is provided. It is also meaningful to consider that attitudes towards medicine and subsequent prescription adherence may be influenced by cultural norms.

Finally, the review is limited by the fact that few of the included articles evaluated the specific indications for both the filled and unfilled prescriptions. This made it impossible to evaluate the prevalence of gender-specific or age-related therapies which may prompt prescription nonfulfillment and explain the significance of age and gender in terms of adherence. This also precluded any evaluation of which factors were associated with the most clinically significant instances of non-redemption.

Conclusion

Given the heterogeneity of the studies identified in this investigative review, it is unsurprising that no strong conclusions can be made at this time regarding the predictors and causes of primary non-adherence. Nonetheless, this study clearly illustrates that many factors warrant further

investigation regarding potential associations with prescription non-fulfillment. The number of contributing factors is vast, and the health care implications are even vaster. Future studies may find it more effective to focus on the unique and individual factors contributing to non-adherence, but the evidence to-date suggests a more systemic problem exists. Future studies will only help to unravel the mysteries of non-adherence. After all, better adherence will lead to an increase in treatment, which in turn will result in better health outcomes, not just for individuals, but for groups, communities and entire health care systems.

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