A Systematic Literature Review of Psychosocial and Behavioral Factors Associated with Initial Medication Adherence: A Report of the ISPOR Medication Adherence & Persistence Special Interest Group

John E. Zeber, PhD[1,2],*, Elizabeth Manias, PhD[3], Allison F. Williams, PhD[4], David Hutchins, MHSA, MBA[5], Waka A. Udezi, PhD[6], Craig S. Roberts, PharmD, MBA[7], Andrew M. Peterson, PharmD, PhD[8], ISPOR Medication Adherence Good Research Practices Working Group

[1]Central Texas Veterans Health Care System, Temple, TX, USA; [2]Scott & White Healthcare, Center for Applied Health Research, Temple, TX, USA; [3]University of Melbourne, Melbourne, Australia; [4]School of Nursing and Midwifery, Monash University, Victoria, Australia; [5]CVS Caremark, Scottsdale, AZ, USA; [6]University of Benin, Benin, Nigeria; [7]Pfizer Inc., Health Economics and Outcomes Research, New York, NY, USA; [8]University of the Sciences, Philadelphia, PA, USA

A B S T R A C T

Objectives: Numerous factors influencing medication adherence in chronically ill patients are well documented, but the paucity of studies concerning initial treatment course experiences represents a significant knowledge gap. As interventions targeting this crucial first phase can affect long-term adherence and outcomes, an international panel conducted a systematic literature review targeting behavioral or psychosocial risk factors. **Methods:** Eligible published articles presenting primary data from 1966 to 2011 were abstracted by independent reviewers through a validated quality instrument, documenting terminology, methodological approaches, and factors associated with initial adherence problems. **Results:** We identified 865 potentially relevant publications; on full review, 24 met eligibility criteria. The mean Nichol quality score was 47.2 (range 19–74), with excellent reviewer concordance (0.966, $P < 0.01$). The most prevalent pharmacotherapy terminology was initial, primary, or first-fill adherence. Articles described the following factors commonly associated with initial nonadherence: patient characteristics ($n = 16$), medication class ($n = 12$), physical comorbidities ($n = 12$), pharmacy co-payments or medication costs ($n = 12$), health beliefs and provider communication ($n = 5$), and other issues. Few studies reported health system factors, such as pharmacy information, prescribing provider licensure, or nonpatient dynamics. **Conclusions:** Several methodological challenges synthesizing the findings were observed. Despite implications for continued medication adherence and clinical outcomes, relatively few articles directly examined issues associated with initial adherence. Notwithstanding this lack of information, many observed factors associated with nonadherence are amenable to potential interventions, establishing a solid foundation for appropriate ongoing behaviors. Besides clarifying definitions and methodology, future research should continue investigating initial prescriptions, treatment barriers, and organizational efforts to promote better long-term adherence.
Keywords: behavioral risk factors, first fill medication adherence, initial medication adherence, primary medication adherence, systematic review.

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Introduction

Medication adherence is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regime" [1]. There are two types of medication adherence: initial adherence, where the patient fills the medication the first time it is prescribed, and continued adherence, where the patient continues to refill the medication. Numerous factors pertaining to poor medication adherence in general for chronically ill patients are well documented. Although a comprehensive list of potential influences would include hundreds of barriers, McHorney [2] summarized the proximal drivers of self-reported adherence problems: 1) perceived drug harms versus benefits, 2) the need for their medication, and 3) out-of-pocket pharmacy costs. There

exists, however, a paucity of studies concerning experiences during the very beginning of the treatment course (often referred to as either "primary, initial, or first-fill adherence"), representing a crucial knowledge gap in understanding why patients choose to begin taking medication. Accurately determining the rate of initial adherence is a challenge, because there is currently no validated, systematic means of determining this process through existing records. Nevertheless, it was estimated that in a national study comprising the vast majority of retail pharmacy prescriptions in the United States, the prevalence of new-fill abandonment was 6.3% in 2009, up from 5.1% the prior year [3].

A challenge with evaluating initial adherence stems from an inability to connect the actions that occur in the prescriber's office with the patient's actions outside the office. Although this

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disconnect may decrease with the rise of new technologies such as electronic systems linking medication prescribers with dispensers more efficiently, at present there are few studies that have attempted to measure initial adherence let alone rigorously define it or summarize factors that influence this issue. In a survey of more than 9000 patients, the Boston Consulting Group reported that 18% of the patients did not fill a prescription in the past 12 months, with 10% giving as a primary reason for nonadherence that they "can't get prescription filled, picked up or delivered" [4]. Other small, nongeneralizable studies about the rate of initial adherence do exist, but these are insufficient to establish a true estimate of the rate of initial nonadherence. These studies have studied either only specific conditions such as asthma [5] or specific settings such as pharmacies [6]. Further complicating the picture are the various definitions used to describe initial medication behavior. Initial nonadherence can be when a patient fails to present a prescription to the pharmacy after it has been first ordered by the health care provider, or neglects to claim a prescription after it has been filled by the pharmacist.

Initiating a medication regimen (i.e., initial adherence) may be the beginning of a complex series of behavior changes that can have a long-term effect on a patient's health and well-being. Therefore, understanding factors that influence this initial behavior can enable the clinician and the health system to identify targeted interventions at this crucial stage in the treatment process to improve the patient's adherence behaviors and longer term outcomes. To that end, the Medication Adherence and Persistence working group of the International Society of Pharmacoeconomics and Outcomes Research undertook this systematic review of the literature to identify the current state of research in this area. The aims of this analysis were to summarize the current body of literature focused on how researchers are currently using terminology for initial medication adherence (and internal consistency within their studies), identify the research strengths and gaps, document potential behavioral or psychosocial risk factors associated with poor adherence during this early treatment phase, and offer recommendations for further research in this area.

Methods

An international panel of researchers with considerable expertise in medication adherence began the process of selecting relevant articles by conducting a comprehensive, systematic review of the published literature, and then documented risk factors related to initial nonadherence. This literature search spanned multiple databases covering the period from 1966 through July 2012 and included Medline (PubMed, Ovid), the Cochrane Library, PsycInfo, Scopus, Web of Science, Embase, and CINAHL. The following standardized search terms were used, all in conjunction with and without the term medication, along with "treatment," "pharmacy," and "prescriptions": primary, initial (non)adherence, primary, initial (non)compliance, and first fill adherence/compliance, In addition to the general term of "risk factor," these key terms were cross-referenced with a lengthy list of potential factors documented to be associated with poor adherence, or conversely, better adherence. These included items such as patient characteristics, medication beliefs, cost, and number of health conditions or comorbidities. Given the multitude of possible key terms and related concepts, please refer to the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.04.014 for additional details concerning our search terms and overall strategy. We also iteratively searched the bibliographies of included articles as well as relevant review articles for additional eligible publications; this follow-up effort yielded approximately 20 potentially new articles, but none that met final inclusion criteria.

Limiting the selection to English publications, we required that the studies conducted work on primary data analysis, with additional exclusions made for case series with fewer than 10 patients, or articles presenting conceptual or theoretical work. To restrict our focus on a limited definition of initial adherence as defined by the study authors, further discussions and a complete review of articles led to excluding those dealing with adherence during the early treatment course or longitudinal persistence, rather than factors associated with the very first prescription. These criteria were applied during the review of the article titles, key words, our initial review of abstracts, and during the thorough full-text review.

Articles meeting final eligibility requirements were then assessed by two independent reviewers through a validated quality instrument documenting methodological details; the Nichol tool evaluates multiple dimensions of research quality, including study design, how disease conditions were defined, and descriptions of adherence measurement [7]. Scaled scores are assigned to a range from 0 to 100, and we report the mean and variance for all included articles. Each article was then fully extracted by at least two independent reviewers to document information concerning adherence definitions (e.g., primary, initial, and other), study type (randomized controlled trial, observational, prospective), the pharmacy data collection method (ordered prescriptions vs. filled claims, or patient self-report), methodology concerning adherence measurement (e.g., number of fills within 90 days, medication possession ratio [MPR], and other techniques), acute and/or chronic disease state and specific diagnoses, and therapeutic drug class. Additional information was collected on patient demographics (including race/culture, socioeconomic status [SES], health literacy), practitioner type (primary care, specialist, nurse practitioner, etc.), prescribing system (electronic, paper), location of dispensing pharmacy (HMO, chain, community), and patient insurance type and/or pharmacy co-payments. Finally, as the primary outcome of interest for this review, significant factors affecting initial adherence were summarized, based on the statistically significant results as reported by the study authors, along with observations concerning study limitations.

After the comprehensive data extractions were completed and new searches revealed no further included articles, the study team again reviewed and summarized these data to confirm a final inclusion list, discuss terminology and central themes, and resolve potential conflicts between reviewers. We also present the most prevalent factors examined in these studies and the reported association with nonadherence, and summarize relative effect sizes determined by the authors. Because relatively few articles also examined the association between initial adherence and other clinical outcomes, these are noted as a secondary aim with further discussion of this implication of medication behavior.

Results

Search Results

Overall, the search identified 865 potentially relevant articles, of which 307 abstracts were deemed eligible for review of additional details. The most common exclusion reason by far was an obvious lack of focus on initial adherence (n = 198), despite implying such an objective in the publication title or key words. Other exclusions included articles not analyzing unique primary data [8], smaller case series [9], conceptual or theoretical articles [10], and non-English articles [3]. Therefore, only 63 articles were