Synthesizing and Appraising the Quality of the Evidence on Factors Associated with Medication Adherence in Diabetes: A Systematic Review of Systematic Reviews

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A B S T R A C T

Background: Nonadherence to medications is a common phenomenon in patients with diabetes. Several studies and systematic reviews have investigated the barriers to medication adherence in diabetes. However, no study has evaluated the quality of the existing literature and synthesized the plethora of evidence with a goal to design holistic conceptual frameworks and interventions. **Objectives:** The aims of this review were to systematically evaluate existing systematic reviews focusing on factors associated with medication adherence in diabetes in an effort to synthesize the evidence, determine their methodological quality, and identify the gaps in the current literature. **Methods:** Fourteen databases and gray literature sources were systematically searched through June 2016. Systematic reviews reporting factors associated with medication adherence (barriers and facilitators) in patients with diabetes were selected on the basis of predetermined criteria. Studies were appraised for quality using AMSTAR (A Measurement Tool to Assess Systematic Reviews). **Results:** Seventeen systematic reviews including 542 primary studies, most of which were cross-sectional quantitative studies, were included. All the reviews were rated as moderate to low quality and exhibited common methodological pitfalls. Factors influencing medication adherence identified were categorized as patient-, medication-, disease-, health care provider–, health care system–, and social-related factors. **Conclusions:** Factors influencing medication adherence are multifactorial with remarkably consistent findings across the existing reviews; yet, most reviews were judged to be of low to moderate quality. Further comprehensive and well-conducted original studies and systematic reviews on this topic shall be conducted taking into consideration the drawbacks of existing ones.

Keywords: diabetes, barriers, facilitators, medication adherence, quality of evidence, systematic review of systematic reviews.

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Introduction

Diabetes mellitus (DM) is considered a burdensome disease globally. In 2014, it was estimated that 307 million people were diagnosed with DM worldwide, a number that is expected to rise to 592 million by 2035 [1,2]. Not only does DM affect patients with the condition, but it also adds to the health care expenditure and burden to the society. Around US $612 billion was spent on diabetes in 2014 alone, a number that is expected to increase to US $627 billion by 2035 [2]. It is well known that poorly controlled diabetes can result in serious complications ranging from microvascular and macrovascular complications to possible hospitalizations, and mortality [1–5].

Nonadherence to oral and/or injectable medications in patients with diabetes presents a major barrier to treatment success [6–8]. Adherence is defined by the World Health Organization as "the extent to which a person's behavior – taking medications, following a diet and/or executing lifestyle changes – corresponds, with agreed recommendations from health care providers" [9]. To successfully manage diabetes, patients need to adhere to drug therapy, dietary requirements, regular exercise, and monitoring. All these measures may be overwhelming to the patient, especially at the initial stage of being diagnosed with the disease. Numerous interventions have targeted improving medication adherence [10–13] with modest success. Such interventions included medication coaching on medication adherence and the use of automated phone calls or mobile phone applications and text messages as patient reminders for their medication dose [10–13]. The World Health Organization emphasized that having well-designed interventions to target medication adherence may have a far greater outcome than the medical treatment itself [9]. Several systematic reviews evaluated the intervention strategies directed toward improving medication adherence in diabetes and have indicated that the interventions

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were labor-intensive, had limited efficacy, and have shown inconsistent results [14–18]. To design effective intervention models, it is imperative to understand the root cause of the problem and determine the full spectrum of the barriers to and factors influencing medication adherence in diabetes.

Furthermore, several original investigations and systematic reviews have been conducted pertaining to medication adherence in diabetes. Therefore, it may not be a prudent and viable investment to reinvent the wheel. Nonetheless, they mainly focused on type 2 diabetes or on multiple chronic disease conditions, thus neglecting type 1 diabetes [19–23]. Another major limitation of the existing systematic reviews is the lack of risk of bias assessment of included studies, making them highly prone to misguided judgments [20,21,24–27]. Furthermore, the methodological qualities of the published systematic reviews have not previously been evaluated. These reviews report a remarkably diverse complex network of factors associated with medication adherence, making it challenging to develop holistic evidence-based interventions without synthesizing the evidence.

Multiple systematic reviews are available on the topic, necessitating synthesis and evidence appraisal to answer the question: What are the factors associated with medication adherence in patients with diabetes and what is the quality of the evidence reporting those? Hence, a review of the systematic reviews will bring together and appraise the existing evidence [28]. This is a multiphase project directed toward the development of a holistic conceptual framework that addresses the complex network of barriers to medication adherence in diabetes. This phase of the project is aimed at systematically evaluating the methodology of existing systematic reviews on medication adherence in patients with diabetes in an effort to synthesize the evidence and identify the gaps in the literature. The review will benefit health care providers in identifying the most reliable evidence to apply in

practice and at the same time provide an insight for researchers about the limitations of the existing studies to avoid in future research studies.

Methods

Data Sources and Search Strategy

A comprehensive systematic literature search was conducted to identify existing systematic reviews addressing factors associated with medication adherence in patients with diabetes. We searched the following databases and online resources to ensure the comprehensiveness of the search: PubMed, Cochrane Library, Campbell Library, Database of Abstracts of Reviews of Effects,

Table 1 – Search terms.

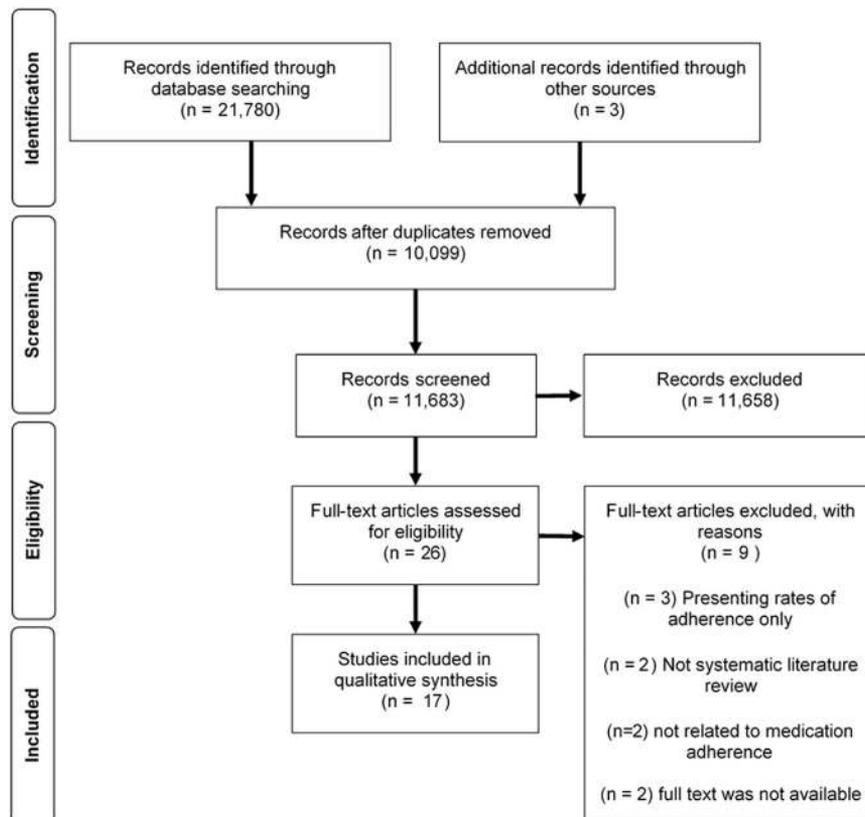| Category	Search terms
Category A	Adheren* – complian* – noncomplian*– nonadhere – non-complian* – non-adheren* – refuse – refusal – comply – complying – adhering – medication adherence – patient compliance
Category B	Diabetes – diabetes mellitus – type 1 diabetes – type 2 diabetes – DM
Category C	Factor – barrier – challeng* – determinant – behavior – predict* – facilitator
Category D	Review – systematic – summary – narrative – mixed method – mixed studies – integrative – literature – meta analysis – overview – rapid review – scoping review – systematized – umbrella review

Fig. 1 – Articles flow diagram.

Table 2 – Characteristics of included systematic reviews.

Reference/ year of publication	Time frame of searches and date range of included studies	Population	No. of studies included	Types of included studies	Location of primary studies	Adherence factors evaluated
Capoccia et al. [37] (2016)	2007–2014 Range: 2007–2013	Adults with type 1 or type 2 diabetes	98	Prospective and retrospective	Not indicated	• Patient-related factors: demographic characteristics, physiological status, health literacy, adapting to changes • Medication-related factors • Provider-related factors • Societal-related factors • Health system–related factors
Tiktin et al. [38] (2016)	2008–2013 Range: 2009–2013	Adults with type 2 diabetes	30	Clinical trials and comparative studies	United States, England, the Netherlands, Mexico, Korea, Denmark, Belgium	• Patient-related factors: demographic characteristics, physiological status • Medication-related factors • Disease-related factors • Provider-related factors
Brundisini et al. [39] (2015)	2002–2013 Range: 2002–2013	Adults with type 2 diabetes	86	Qualitative; interviews, focus groups	United States, England, Canada, the Netherlands, Australia, Norway, Sweden, Belgium, Croatia, Germany, Romania	• Patient-related factors: physiological status, health literacy, emotions, perceptions, adapting to changes • Medication-related factors • Disease-related factors • Provider-related factors • Societal-related factors
Krass et al. [19] (2015)	2004–2013 Range: 2004–2013	Adults with type 2 diabetes	27	Retrospective, prospective, and cross-sectional studies	United States, Iran, the Netherlands, Malaysia, France, Korea, Sweden, Japan, Germany, Palestine, Egypt, Nigeria	• Patient-related factors: demographic characteristics, physiological status • Medication-related factors • Disease-related factors • Health care system–related factors
Sohal et al. [23] (2015)	1990–2014 Range: 1994–2013	Adults with type 2 diabetes	20	Qualitative (interview or focus group), cross-sectional, and mixed method	United States, England, Scotland, India, Norway	• Patient-related factors: health literacy, perceptions, adapting to changes • Medication-related factors • Societal-related factors
Al Hamid et al. [40] (2014)	1990–2014 Range: 2004–2013	Adults with cardiovascular diseases or diabetes	21 (15 diabetes related)	Focus groups and interviews	England, Scotland, Canada, Australia, Malaysia, Spain, South Africa, Taiwan, Croatia, Cameron, Brazil, Ireland	• Patient-related factors: physiological status, health literacy, perceptions, adapting to changes • Medication-related factors
Davies et al. [41] (2013)	Inception–2011 Range: 1986–2012	Adults with type 1 or type 2 diabetes	17	Mixed (cross-sectional, retrospective, and prospective studies)	England, Scotland, Mexico, New Zealand, South Africa	• Patient-related factors: demographic characteristics, health literacy, perceptions • Medication-related factors • Disease-related factors • Health care system–related factors
Polinski et al. [20] (2013)	Inception–2011 Range: 1999–2011	Adults with type 2 diabetes	10	Cross-sectional studies, randomized controlled studies, and quasi design	Africa, Middle East, Asia, Eastern Europe, Latin America, Canada, Germany, Japan, Spain, Turkey, United Kingdom, United States, Spain	• Patient-related factors: emotions, fear, perceptions • Medication-related factors • Disease-related factors • Societal-related factors

Study	Years	Population	No. of studies	Study design	Countries	Factors
						• Provider-related factors • Health care system–related factors
Sarayani et al. [42] (2013)	Inception–2012 Range: 2002–2012	Adults with cardiovascular disease or diabetes	14 (6 diabetes related)	Cross- sectional studies (questionnaires)	Iran	• Patient-related factors: emotions, fear, adapting to changes • Medication-related factors • Societal-related factors • Health care system–related factors
Peeters et al. [22] (2011)	Inception–2009 Range: 1991–2009	Adults with type 2 diabetes	12	Cross- sectional observational studies	United States, New Zealand, South Africa,	• Patient-related factors: demographic characteristics, physiological status, perceptions, adapting to changes • Health care system–related factors
Gherman et al. [43] (2011)	Inception–2010 Range: 1985– 2010	Adults with type 1 or type 2 or gestational diabetes	48	Cross- sectional studies	United States, Australia, India, Mexico, New Zealand, Turkey, Taiwan, Japan, China	• Patient-related factors: perceptions • Provider-related factors
Nam et al. [21] (2011)	1990–2009 Ranges: 1990– 2007	Adults with type 2 diabetes	80	Cross- sectional observation studies, randomized controlled studies, qualitative studies, retrospective cohort studies, case control studies	Not indicated	• Patient-related factors: demographic characteristics, physiological status, health literacy, emotions, fear, perceptions, adapting to changes • Medication-related factors • Provider-related factors • Societal-related factors • Health care system–related factors
Fu et al. [44] (2009)	1990–2008 Range: 1996–2008	Adults with type 1 or type 2 diabetes	6	Interview survey using questionnaire. Cross- sectional studies and one longitudinal study	United States, England, the Netherlands	• Patient-related factors: fear
Pun et al. [45] (2009)	1986–2007 Range: 1986–2006	Adults with type 2 diabetes and health care provider	16	Quantitative, mixed method, focus groups	United States, England, Mexico	• Patient-related factors: physiological status, health literacy, health literacy, emotions, perceptions • Medication-related factors • Disease-related factors • Provider-related factors • Societal-related factors • Health care system–related factors
Gonzalez et al. [46] (2008)	1950–2008 Range: 1984–2008	Adolescents, or adults with type 1 or type 2 diabetes	47 (18 studies related to diabetes medications)	Cross- sectional or longitudinal	Japan, United States, New Zealand, Mexico, Germany, Canada, Croatia, Korea, England, the Netherlands	• Patient-related factors: physiological status
Lee et al. [47] (2006)	1990–2005 Range: 1999–2005	Adults with type 2 diabetes	27	Prospective and retrospective	United States, Scotland, France, Switzerland	• Patient-related factors: physiological status • Medication-related factors • Health care system–related factors
Nagasawa et al. [48] (1990)	1968–1988 Range: 1967–1988	Adolescents, or adults with type 1 or type 2 diabetes	26	Not indicated	Not indicated	• Patient-related factors: demographic characteristics, health literacy, emotions, perceptions • Societal-related factors

Reference/year of publication	Provides an "*a priori* design"	Duplicate data extraction	Search two or more databases plus another source	Gray literature	Includes a list of included and excluded studies	Reports characteristics of each included study	Assesses and documents scientific quality of included studies	Uses scientific quality of the studies appropriately	Includes conflict of interest statement	Overall rating	Funding
Capoccia et al. [37] (2016)	–	Y	Y	–	–	Y	Y	Y	–	Moderate	None
Tiktin et al. [38] (2016)	–	–	–	–	–	Y	–	–	–	Low	Novo Nordisk Inc.
Brundisini et al. [39] (2015)	Y	Y	Y	–	Y	Y	–	–	–	Moderate	Government of Ontario
Krass et al. [19] (2015)	–	Y	Y	–	–	Y	–	–	–	Low	None
Sohal et al. [23] (2015)	–	–	Y	–	–	Y	Y	Y	–	Moderate	Michael Smith Foundation for Health Research Career Scientist Award and Alberta Innovates Health Solutions Health Scholar Award
Al Hamid [40] (2014)	–	–	Y	–	–	Y	Y	Y	–	Moderate	None
Davies et al. [41] (2013)	–	–	Y	–	Y	Y	Y	Y	–	Moderate	Novo Nordisk Region International Operations
Polinski et al. [20] (2013)	–	Y	Y	–	Y	Y	–	–	–	Moderate	Eli Lilly and Company
Sarayani et al. [42] (2013)	–	Y	Y	Y	–	Y	Y	Y	–	Moderate	None
Peeters et al [22] (2011)	–	Y	Y	–	–	Y	–	–	–	Moderate	Not indicated
Gherman et al. [43] (2011)	–	–	–	–	–	Y	Y	Y	–	Low	Not indicated

Table 3 – Quality assessment of included systematic reviews.

Study										Quality	Source of funding
Nam et al. [21] (2011)	–	–	–	Y	–	Y	–	Y	–	Low	California Endowment and American Association of Colleges of Nursing
Fu et al. [44] (2009)	–	–	–	Y	–	Y	–	Y	–	Low	Merck and Co. Inc.
Pun et al. [45] (2009)	–	–	–	Y	–	Y	–	Y	–	Low	Not indicated
Gonzalez et al. [46] (2008)	–	–	–	Y	Y	Y	Y	Y	Y	Moderate	National Institute of Mental Health
Lee et al. [47] (2006)	–	–	–	Y	Y	Y	Y	Y	–	Low	Novo Nordisk Inc.
Nagasawa et al. [48] (1990)	–	–	–	Y	–	Y	–	Y	–	Low	Diabetes Research and Education foundation

–, No; Y, yes.

Academic Search Complete, EMBASE, Evidence-Based Practice Center Program (EPC), SCOPUS, Health System Evidence, Pro-Quest, ScienceDirect, Global Health Database, Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports, and Google Scholar. This was accomplished by one author (M.J.) and verified by a second author (A.A.). The process also included manual searches of the bibliographies of the articles identified electronically as well as gray literature including abstract of thesis, documents produced by academic institutions, and conference proceedings. The alert systems of the electronic databases, whenever available, were used to receive any relevant new article that fits within our search strategy.

The search terms available from categories A (terms relating to adherence), B (terms relating to diabetes), C (terms relating to factors), and D (terms relating to systematic reviews) in Table 1 were combined differently using Boolean operators (AND/OR) in such a way that all relevant reviews would be retrieved. The four groups of search terms related to 1) adherence to drug therapy; 2) the health condition (i.e., diabetes); 3) factors associated with adherence; and 4) study design (i.e., systematic reviews). Medical subject heading or similar terms were used in corresponding databases as appropriate.

Study Selection

Included articles were systematic reviews published in English language addressing factors associated with medication adherence in patients with diabetes. In addition, systematic reviews that looked at a combination of diseases were included if they analyzed medication adherence in diabetes separately. Studies focusing on substance abusers, patients with mental disorders, tuberculosis, HIV, and gestational diabetes were excluded because each of these population groups has its own circumstances that affect medication adherence. Moreover, narrative reviews not following systematic review or systematic literature search strategy, reviews reporting rates of medication adherence only, reviews investigating the impact of interventions, and comparative reviews were also excluded.

Study Quality and Bias Assessment

The AMSTAR (A Measuring Tool to Assess Systematic Reviews), a quality assessment tool for systematic reviews, was used for evaluating the methodological quality of the included reviews [29]. The original tool has 12 items, each scored as "yes, no, can't answer, or not applicable." Items 9 and 10 were not considered in the present evaluation because they were not applicable to the types of systematic reviews included. These items are directed at the evaluation of meta-analysis and relate to the assessment of heterogeneity and publication bias, respectively. All items of the AMSTAR tool were weighted equally with a quantitative score of 1 for each item. Final grading of the methodological quality was based on the following: 0 to 3, 4 to 6, and 7 to 9 corresponding to "low quality," "moderate quality," and "high quality," respectively. Two reviewers independently scored each of the included reviews. Any disagreements or discrepancies were resolved through discussions and consensus.

Data Extraction and Synthesis

Data were extracted by two independent reviewers using a tool developed and pretested for this purpose. The elements extracted included title, authors, year of publication, primary objective(s) of the review, inclusion and exclusion criteria, article sources including databases, search strategy, bias and quality assessment methodology for included studies, number of included articles, study design of included articles, key findings, conclusion, limitations, source of funding, and quality assessment. In cases in

which a review included multiple disease conditions, only diabetes-related information was extracted. Based on the extracted data, textual summaries and summary tables were developed. From these, emerging categories relating to factors influencing medication adherence were identified.

Results

Study Characteristics

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used in reporting our findings (see PRISMA Checklist S1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2017.04.005). Through searching and after removing duplicates, 11,683 unique references were found of which 26 reviews were potentially relevant based on screening of titles and abstracts. After full-text evaluation, 17 systematic review articles were eligible for inclusion. Two of the potentially relevant reviews were presented as conference abstracts and their full text was not available; therefore, they were excluded from the study [30,31] (Fig. 1). Other studies were excluded for one of the following reasons: not systematic reviews or did not use systematic search strategy [32,33], not related to medication adherence in diabetes [34,35], or presented only rates of medication adherence without its associated factors [24,27,36].

All the included systematic reviews were published in English from 1990 to 2016 covering primary studies published from 1967 to 2016. All the reviews included the details of the primary studies, most of which were conducted in the United States and the United Kingdom, with a wide representation of studies from other countries across the world (Table 2). The total number of diabetes-related studies included in the 17 reviews was 542, with an average of 32 studies per review (range 6–98), most of which were cross-sectional quantitative studies.

Methodological Quality of Included Reviews

The AMSTAR score for the included systematic reviews ranged from 1 to 6 (Table 3). Nine articles were rated as "moderate quality," whereas the rest were rated as "low quality." Overall, the evaluated systematic reviews shared common methodological pitfalls. For instance, none of the reviews had reported conflict of interest related to the primary studies they included, only one had an *a priori* protocol, and only three reported searching the gray literature. Most reviews (11 of 17) did not report assessing the methodological quality of the primary studies they included, but those that assessed the quality did it appropriately. Regarding the source of funding for the reviews, five were funded by Novo Nordisk, Merck and Co. Inc., and Eli Lilly and Company (Table 3).

Factors Associated with Medication Adherence in Diabetes

The reviewed systematic reviews indicate that factors associated with medication adherence are multifactorial with remarkably consistent findings across the reviews. Barriers to or factors associated with medication adherence derived from the included reviews were categorized into the following: patient-, medication-, disease-, care provider–, health care system–, and societal-related factors (Table 4). Given the large variation in patient-related factors and its major subtypes across the reviews, we further classified it using thematic content analysis into several subcategories: demographic characteristics, physiological status, health literacy, emotions, fear, perceptions, and adaptation to changes (Table 4). The most predominantly reported patient-related factors included age, depression, and health literacy level. On the other hand, side effects and frequency of dosing were the most commonly reported medication-related factors. Disease-related factors such as duration of diabetes, disease complexity, and complications were rarely addressed. Societal-related factors commonly identified by the reviews were social stigma, cultural barriers, and lack of support. Moreover, issues surrounding insurance coverage and cost of medicines were among the most frequently identified barriers to medication adherence in the reviewed studies.

Discussion

To our knowledge, this is the first systematic review of systematic reviews to evaluate the overall evidence on the factors associated with medication adherence in both type 1 and type 2 diabetes. Systematic reviews and meta-analyses are generally considered the best sources for evidence-based information. Nevertheless, the value of these studies depends largely on their scientific and methodological quality [49]. Therefore, it is essential for the reader to critically appraise the methodologic quality using appropriate instruments. The AMSTAR tool that we used in this study is a reliable and widely used tool for the assessment of systematic reviews [29–52].

One item of the AMSTAR tool refers to stating conflict of interest of the systematic review itself as well as for all the individually included primary studies, which none of the reviews did. This appears to be similar across similarly conducted systematic reviews, where looking at conflict of interest remains to be underestimated [53]. When further investigated, we noted that two of the reviews had self-citations within the included studies [37,46]. When this is not declared, it may be assumed that the authors may be biased toward their work, which may influence how they rate the quality of their articles.

It is evident that the included reviews have fallen into the common pitfalls of published reviews as recently described by MacLure et al. [49]. The lack of detailed published protocol in most except for one review [39] presents a risk of bias within these reviews. This may probably be related to the nature of the included primary studies, which were not intervention-type studies, or that the importance of publishing a protocol before the conduct of a systematic review might have been underestimated by the authors. Nonetheless, a published protocol would provide an evidence of the reliable conduct of the study.

It is noteworthy that in this review, all the AMSTAR items were assigned equal weight during scoring. However, in our opinion, items relating to the quality assessment of the primary studies as well as comprehensiveness of search applied in the systematic review may be considered the most important elements for systematic reviews and should therefore be given greater weights. Nonetheless, it is worthwhile to note that a new AMSTAR tool that can be used for nonrandomized studies is under development taking into consideration the suggestions and feedback from users. Therefore, the overall scoring of the included reviews may differ accordingly [49].

In addition, the lack of team experience and independent involvement in the methodological process of the reviews is another issue presented in more than half of the reviews included in this study. One major pitfall is the absence of quality assessment of primary studies, which can be considered as a major source of bias [49]. These issues can easily be overcome and avoided with the use of focused and detailed protocol based on existing guidelines in addition to learning from the experience of other researchers.

In addition to the quality improvement needed in the conduct of systematic reviews, we have noted that the Middle East and North African (MENA) region is highly under-represented. We conducted a primary literature search in the same databases

Table 4 – Factors associated with medication adherence in diabetes.	
Factors	**Studies**
Patient-related factors	
Demographic characteristics (age, sex, ethnicity, financial status and level of income, marital status, and level of education)	[19,21,22,37–39,41,47,48]
Physiological status (comorbidities, depression, smoking, and forgetfulness)	[19,21,22,37–40,45,46]
Health literacy (lack of understanding about the disease and treatment, difficulty reading prescription)	[21,23,37,39–41,45,46,48]
Emotions (blame, guilt, shock and helplessness, frustration, negative attitude, stress, and anxiety)	[20,21,39,40,42,45,48]
Fears (injection, blood phobia, and fear of pain)	[20,21,39,42,44]
Perceptions of (need of medicine, barriers to follow medication, benefit from treatment, misconception about medications, and self-efficacy)	[19–23,39–41,43,45,48]
Adaptation to change (traveling overseas, alterations in daily schedule, change or lack of routine in managing treatment, and diet adjustments)	[23,37,39–42]
Medication-related factors	
Frequency of dose or injection	[19,21,37,38,41,47]
Length of therapy	[47]
Number of medications and polypharmacy	[19,22,38,40]
Timing of dosing	[37]
Changing of treatment	[41]
Fluctuating response to medications	[45]
Side effects	[19,20,22,23,37,39,40,42,45]
Complexity of regimen	[20,37,39,40]
Drug class/type	[19,21,22,38,47]
Method of drug administration	[20,38–40]
Traditional medicine and phytotherapy	[23,39,40]
Disease-related factors	
Diabetes duration	[19,38]
Disease complexity	[39,45]
Lower HbA_{1c}	[20,41]
Complications	[19]
Provider-related factors	
Support from health care providers	[37,38]
Patient not included in decision-making process	[37,39]
Duration of counseling and lack of time	[20,38,39]
Relationship with care provider	[21,43]
Assumptions by providers about the patients' knowledge	[20,21,39]
Providing ambiguous or incomplete information	[21,39]
Provider's lack of experience	[20]
Language and communication barrier	[19,21,39,45,48]
Societal-related factors	
Support from family	[21,37]
Lack of support	[21,39,45]
Cultural barriers	[21,39,45]
Stigma	[20,23,39,42]
Health care system–related factors	
Insurance coverage	[19,22,37,41,42,47]
Lack of guidelines about optimal treatment	[20,45]
Cost of medicine	[19,21,39,47]
Co-payment amount	[37,47]
Convenience of obtaining medications	[37,38]
Continuity of care	[37]
HbA_{1c}, glycated hemoglobin.	

used by these reviews and noted many hits within the MENA region. Most of the reviewers did not limit their search to particular countries; therefore, the exclusion of the primary studies from the MENA region cannot be justified.

There are some inherent limitations in the methodology used in this study. Generally, the review relies on information presented by the existing reviews of low to moderate methodological quality, which may undermine the quality of this review. Other limitations to this review include that duplicates of the primary studies within the reviews were not checked. It may therefore be that some evidences were counted more than once. Nonetheless, the primary purpose of this review was to synthesize and assess the quality of the existing evidence. Moreover, the quality of this review depends on the quality of the primary studies within the included reviews. Not all reviews have assessed the quality of their included studies; thus, the summary of the factors associated with medication adherence in diabetes may not be as well founded.

Conclusions

Our search indicates that the topic of medication adherence in patients with diabetes has been extensively studied and published in the literature. The findings of the review suggest that factors associated with medication adherence in diabetes are multifaceted with remarkably consistent findings across the existing systematic reviews; yet, the reviews were judged to be of moderate to low quality. Further comprehensive and well-designed original investigations and systematic reviews on this topic shall be conducted, taking into consideration the pitfalls of the existing ones. This review has been the guiding principle for developing a holistic conceptual framework that will address the complex network of barriers to medication adherence in diabetes.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2017.09.001 or, if a hard copy of article, at www.valuein healthjournal.com/issues (select volume, issue, and article).

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