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Pharmacy-led interventions to improve medication adherence among adults with diabetes: A systematic review and meta-analysis

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ABSTRACT

Background: Control of blood glucose and a reduced risk of complications are important treatment goals in diabetes. Medication non-adherence can influence the outcome of diabetes. Involvement of a pharmacist in diabetes care might help patients to achieve better treatment outcomes. Existing literature reviews have focused on a limited number of interventions and outcome measures, and have involved different healthcare professionals. None of the previous reviews have used a standardized effect size to compare the effects of different pharmacist-led interventions and different outcome measures.

Objective: To review pharmacist-led interventions to improve medication adherence in patients with diabetes and to assess the effectiveness of these interventions on medication adherence.

Methods: Six databases were systematically searched between March and September 2017 for randomized controlled trials: PubMed, Cochrane library, EMBASE, CINAHL, JSTOR, and Web of Science. The outcome measures used were: medication adherence, HbA1c, fasting plasma glucose (FPG), post-prandial blood glucose (PPG), or random blood glucose (RBG). Cohen's d, a standardized effect size, enabled a comparison of studies with different outcome measures. The Cochrane risk of bias tool was used to assess the quality of the studies.

Results: Fifty-nine studies were included in this review. Pharmacist-led interventions enhanced outcomes in patients with diabetes (standardized mean difference (SMD) −0.68; 95% CI -0.79, −0.58; $p < 0.001$). Subgroup analysis by intervention strategy, the type of intervention and outcome measures produced similar results. Further analysis showed that education, printed/digital material, training/group discussion, were more effective than other interventions.

Conclusion: This finding supports the role of the pharmacist in diabetes care to enhance medication adherence.

Introduction

Diabetes is a global health problem with an increasing prevalence. The World Health Organization (WHO) has estimated that in 2014 about 420 million people in the world had diabetes.[1] According to the International Diabetes Federation (IDF), this number has increased by around 5 million in 2017.[2–4] If this trend continues, the number of patients with diabetes is expected to reach 629 million people in 2045.[4] The high risk of complications (microvascular and macrovascular) increases morbidity and mortality risks among people with diabetes.[1–5] As a consequence, higher expenditures on diabetes care are unavoidable. Optimal management of diabetes management is essential to contain the increased cost. In total, 727 billion USD was spent on diabetes and the complications of diabetes in 2017.[4] This accounted for 6–17% of total health expenditure in the IDF region.[4]

Control of blood glucose and reduced risk of diabetes complications are the primary goals of medication treatment for diabetes.[6] Medication adherence is critical for optimal treatment of diabetes. Adherence is defined as “the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider”.[7] Adherence is influenced by several factors including therapy management (complexity of treatment, duration of therapy, medication side effects, time per day spent on treatment), the health care system (quality of the patient–care provider relationship, access care), as well as factors related to the individual patient and their close relatives, demographic,

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socioeconomic and disease-related factors.[8,9] Despite the importance of medication adherence in diabetes, evidence has shown that adherence to diabetes treatment ranges between 36 and 93%.[10,11] Non-adherence could result in sub-optimal control of diabetes that could increase the disease burden.[12,13] Improvement in adherence is expected to lower health care expenditures, reduce glycosylated A1C (a blood test analysis to monitor blood glucose control during the previous two or three months), and the risk of complications.[9,14]

Health care professionals play an important role in improving adherence among patients with diabetes. With so many healthcare professionals involved in patient care, collaboration and a multidisciplinary approach are recommended by diabetes guidelines to provide a more holistic treatment and to obtain better outcomes.[6,15] A larger role of the pharmacist, i.e. the transition from product oriented to patient care oriented services (including education, monitoring treatment goals, adherence, drug-related problem assessment), can improve patients' medication adherence and can result in better treatment outcomes.[16] Also, the involvement of a pharmacist in a diabetes multidisciplinary healthcare team is recommended by several studies[17–19] including those by the American Diabetes Association (ADA) and the Canadian Diabetes Association.[6,15] Previous literature reviews have shown that pharmacist-led interventions could help reach the glycemic goal and improve medication adherence.[20–28] However, they either have a narrow scope, e.g. they focus on a limited number of interventions and outcome measures, or are too broad, e.g. they involve various interventions by health care professionals and not only those by pharmacists. This paper provides a systematic review of pharmacists' interventions to improve medication adherence in patients with diabetes, and assesses the effectiveness of these interventions. This effectiveness can be measured through blood analysis tests, with different outcome measures, namely HbA1c, fasting plasma glucose (FPG), post-prandial blood glucose (PPG), or random blood glucose (RBG). The effectiveness can also be measured through non-blood analysis tests, for example by a questionnaire, which measures the outcomes of an intervention in terms of stated medication adherence. In contrast to prior studies that have compared the effects of interventions using different outcome measures, the present study uses Cohen's d to standardize effect size measures. Standardized effect size measures enable a meta-analysis and meta-regression analysis comparing studies with different intervention strategies, types of interventions and outcome measures.

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis [PRISMA] guideline.[29] The systematic review was registered with the Prospective Registration of Systematic Reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=76905), as PROSPERO 2017: CRD42017076905.

Search strategy

Six databases (PubMed, Cochrane library, EMBASE, CINAHL, JSTOR, and Web of Science) were searched from March until September 2017. The search started with an initial search in March; a final search in April and the last check for updates in September 2017. The three main keywords used were “diabetes”, “medication adherence” and “pharmacist”. They were combined using Boolean Operator (AND, OR, NOT). Medical subject subheading (MeSH) terms and EMTREE (a hierarchically structured, controlled vocabulary used to index all of the EMBASE content) were used for the search in PubMed and EMBASE respectively.

The final search terms used in PubMed were as follows:

(“diabetes mellitus" [MeSH Terms] OR (“diabetes" [All Fields] AND “mellitus" [All Fields]) OR “diabetes mellitus" [All Fields] OR “diabetes" [All Fields] OR “diabetes insipidus" [MeSH Terms] OR (“diabetes" [All Fields] AND “insipidus" [All Fields]) OR “diabetes insipidus" [All Fields]) OR (“diabetes mellitus, type 2" [MeSH Terms] OR “type 2 diabetes mellitus" [All Fields] OR “diabetes type 2" [All Fields]) OR (“diabetes mellitus, type 1" [MeSH Terms] OR “type 1 diabetes mellitus" [All Fields] OR “diabetes type 1" [All Fields]) **AND** (“pharmacists" [MeSH Terms] OR “pharmacists" [All Fields] OR “pharmacist" [All Fields]) **AND** (“medication adherence" [MeSH Terms] OR (“medication" [All Fields] AND “adherence" [All Fields]) OR “medication adherence" [All Fields])

This set of search terms was slightly modified when searching in other databases due to a different system and technical limitations (Table 1).

Table 1
Search strategy in other databases.

Databases	Searching strategy
EMBASE	Three main keywords (diabetes AND pharmacist AND medication adherence) using a combination of multi-field search in all fields and EMTREE (exp diabetes mellitus/AND exp pharmacist/AND exp medication compliance/)
Cochrane	Three main keywords (diabetes AND pharmacist AND medication adherence) in title, abstract and keyword
CINAHL	Three main keywords (diabetes AND pharmacist AND medication adherence)
JSTOR	Three main keywords (diabetes AND pharmacist AND medication adherence) in advanced search
Web of Science	Three main keywords (diabetes AND pharmacist AND medication adherence) in basic search

Study selection criteria

Studies were included if they were based on a randomized controlled trial that evaluated an intervention by a pharmacist with the aim to improve medication adherence among adult patients with diabetes. Studies were excluded if the intervention was carried out by a healthcare professional other than a pharmacist and if the treatment group consisted of pediatric or adolescent patients with diabetes (less than 18 years old). Outpatient care was the main focus of this review without any limitation on the setting (hospital, clinic or community). Studies that solely focused on inpatient care were excluded. The outcome measures used in this review included at least one of following: medication adherence, glycosylated haemoglobin (HbA1c), fasting blood glucose (FPG), post-prandial blood glucose (PPG), or random blood glucose (RBG). There was no restriction on the year of publication but only English language published studies were included in this systematic review.

The study selection followed three steps. First, one of the researchers screened all titles and abstracts; and consulted with the two other researchers when there was a problem with the selection of a study. Second, potential studies included during the first step; were further screened for relevance by assessing the full-text version based on inclusion criteria and in consultation with the two other authors. If a conference abstract was found, we tried to find the full-text version for this abstract. Third, the reference lists of the selected publications were reviewed.

Study extraction and analysis

One of the researchers extracted the data from the studies included in this review. No blinding for author or journal was applied in the extraction process. Data extracted were publication details (title, author, year of publication, and journal name); study design characteristics (country setting of the study, type of the study, study objective, random allocation, period of study conducted and sample size); study characteristic (age, period of follow up, types of outcomes measures, types of tools used to measure outcome, intervention strategy and type of individual intervention), and results of the study.

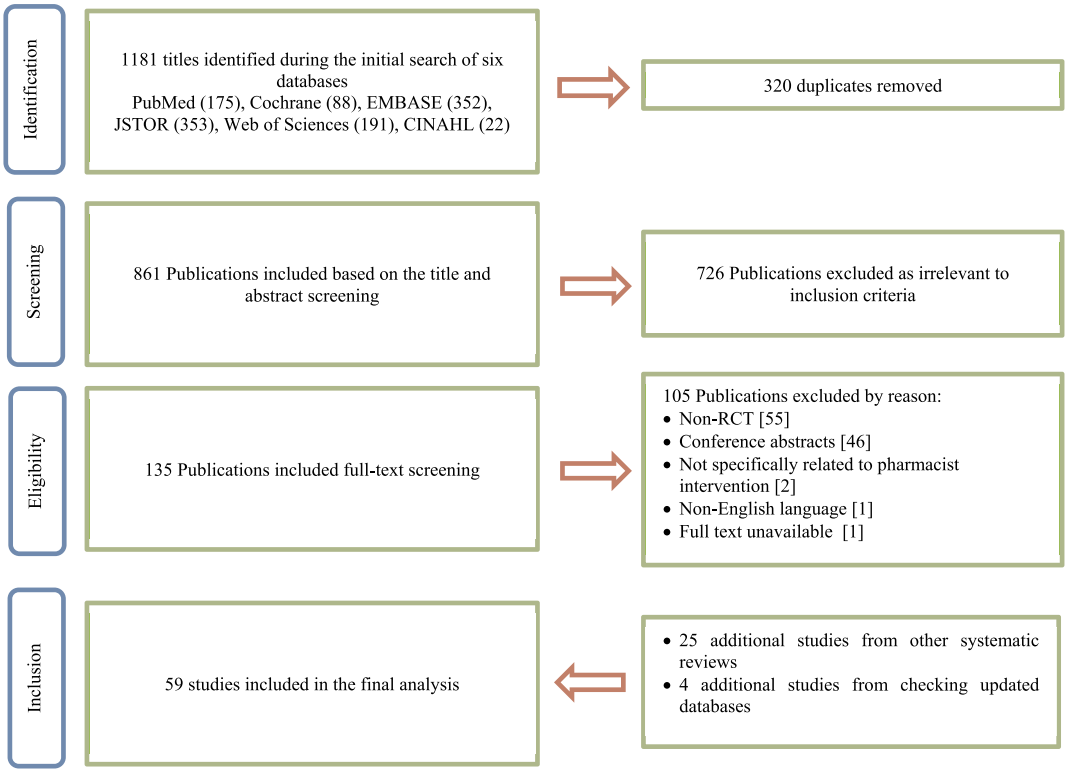

Fig. 1. Flowchart of study selection.

The baseline and follow-up mean values of the outcome measures are reported in the review and are used to measure the effectiveness of the intervention. Changes in values (follow-up minus baseline value for each group) were used if the baseline and follow-up values were unavailable. Based on the forest plot and funnel plot diagram, studies with more than a 4-point difference in the effect size value compared to the average effect size, were categorised as outliers and were excluded from the analysis. No indication of a more suitable cut-off point was found in the literature. Meta-analysis using a random effect model was applied to the pooled data. Standardized effect sizes using Cohen's d with 95% CI were also automatically calculated when the meta-analysis was applied (mean and SD value were available).[30] Sub-group meta-analysis was done based on the period of follow up, types of outcome, and types of intervention. These results are presented in tables and forest plots. Meta-regression was also applied to explore which characteristics were associated with the effect size. All analyses were carried out using Stata version 15.0. The PRISMA checklist was used as a guide for checking the quality of our systematic review.

Risk of bias assessment

The Cochrane risk of bias tool (RoB 2.0) was used as the primary tool to assess the quality of the studies.[31] One researcher assessed the risk of bias and discussed with the other two researchers when problems were encountered. The assessment includes 5 domains: the randomization process, deviation from the intended intervention, missing data outcome, measurement of outcome, and selection of the reported result. Categories used were “low risk” if it was not likely to influence the result; “some concern” if there was some doubt about the result; and “high risk” if there was a high concern on the result.

Results

The search in all databases resulted in a total of 1181 titles. After title and abstract screening, 135 studies met the inclusion criteria and were explored further by reading the full-text. This further screening took out 105 of the 135 and left 30 studies that met the inclusion criteria. Non-randomized controlled trials and full-text unavailability (mostly conference abstracts) were the two main reasons studies were excluded. Some of the conference abstracts came up during the search process. The search process also included other systematic reviews to get other randomized controlled trials that did not show up in the search strategy. This resulted in another 25 studies included in this systematic review. A final check on the updated studies in all databases in September 2017, added another 4 studies. A total of 59 studies were included in this systematic review (Fig. 1).

Study characteristics

The studies included in this review, cover countries from all six continents. Twenty-seven studies were conducted in Asia; 17 studies in North America; 7 in Europe; 4 in South America; 2 in Australia; and 2 in Africa. The study settings were clinics, community pharmacies and hospitals. Three intervention strategies were distinguished: educational, behavioral, and combined (educational and behavioral) interventions. Various types of pharmacists' interventions were found, such as education, consultation, medication review, printed/digital material, telephone calls, daily record books, training and group discussions, and other (referrals, blood glucose meters, and pillbox). Interventions were implemented separately or as a combination of interventions. Four outcome measures based on blood analysis test were reported in the studies reviewed. Specifically, 46 studies reported on HbA1c; 26 studies on FPG; 4 studies on PPG; 4 studies on RBG. An additional outcome measure, reported in 28 studies, was medication adherence measured based on a questionnaire. Some studies showed that pharmacists contacted a physician if there was a need for approving medication modification. In three studies, pharmacists also involved a dietician, nurse and physician for some parts of the intervention.[32–34] Details of the study characteristic are presented in Table 2. A description of the studies included in this systematic review can be found in Appendix 1.

Study quality assessment

The quality assessment of the studies using the Cochrane risk of bias tool showed some concern and a moderate risk of bias in 38 studies while 21 studies had a high risk of bias in quality. This assessment did not find a study with a low risk of bias in quality. The two domains that mostly contributed to the moderate and high risk of bias were the "randomization process" and "deviation from the intended intervention".

Also, allocation concealment and blinding among groups were mostly under-reported in the studies. A lack of information on allocation concealment was found in 48 studies, 56 studies did not provide information about blinding on the patient side, and 51 studies did not provide information about the blinding of the pharmacist who provided the intervention. An unbalanced number of patients across the treatment and control groups was found in 13 studies.

Funnel plots showed that the results might be influenced by publication bias (Appendix 2). The Egger's test showed that the effect size measures reported in this study may be affected by the effect size measures of small studies (Egger's bias coefficient −3.123, 95% CI -5.007, −1.239, P = 0.001).

Overall pooled effect size

Based on the preliminary assessment of the pooled effect size estimation of the overall study results, two studies[38,39] were excluded from the analysis. These two studies appeared to be outliers based on the preliminary forest plot diagram and pooled effect size estimation: their effect size was considerably different from the effect size reported in other studies (more than a four-point difference in value between studies).

Fig. 2 presents the overall pooled effect size estimation of the interventions reviewed in the studies, on the outcome measures when the studies were analyzed together using a random effect model. For this purpose, the effect size values of the medication adherence were taken with a negative sign to be comparable to the values of the other four outcome measures. Thus, in this pooled analysis, a negative overall effect indicates an improvement. As shown in the figure, the pooled results from all studies indicate a significant improvement in the outcome measures by the intervention in general (SMD/standardized mean difference −0.69; 95% CI -0.79, −0.58; P < 0.001).

Effect of follow-up period and intervention strategy on the outcome measures

Random effect models by outcome measure (medication adherence, HbA1c, FPG, PPG, RBG) were also applied to estimate the effect size for subgroups of studies, based on the follow-up period and the intervention strategy. Some studies were included in more than one subgroup because they had more than one period of follow up and/or included a combination of more than one intervention strategy. In the analysis of the total effect size (including all outcome measures) for each period of follow-up and intervention strategy, a modification of the sign of the medication adherence value was applied, namely, the effect size value of the stated medication adherence was modified into a negative sign.

Table 3 presents a summary of the pooled effect size estimation based on the follow-up period and intervention strategy. As indicated in the table, pharmacists' interventions significantly improved almost all outcome measures within three time periods of follow up. The analysis on each group based on the intervention strategy, also showed a similar effect on the outcome measures (stated medication adherence, HbA1c, and blood test other than HbA1c (FPG/PPG/RBG)).

As indicated in the table, a combined intervention strategy (including both educational and behavioral elements) was the most popular strategy used by pharmacists. The educational intervention strategy was also frequently applied alone. Both strategies significantly improved all outcome measures. These strategies were realized using various types of interventions. Based on an additional table in Appendix 3, the five most common types of individual interventions used by the pharmacist were education, consultation, printed/digital material, medication review and telephone call. These pharmacist-led types of individual interventions significantly improved the overall outcome measures of a patient with diabetes, even though there was a non-significant result on one of the outcome measures (training/group discussion on blood test other than HbA1c). Some of the data on interventions and outcome measures could not be analyzed because of a lack of studies. The forest plot for the period of follow-up, intervention strategy and type of intervention can be found in Appendix 4-6.

Analysis of the effect of study characteristics on the effect size

Meta-regression analysis was done to explore the association between the study characteristics and the effect size. Again, modification of the sign of the medication adherence value was done to make it comparable with the other outcome measures.

Table 4 presents a summary of the results of the meta-regression analysis. Seven meta-regression models were estimated: one model with the outcome measures as an explanatory variable (model I), one model with type of intervention as variables (model II), one model with intervention strategy (model III), one model with continent (model IV), one model with other characteristics besides the outcome measure, intervention strategy and type of intervention (model V), a full model that included all variables using the intervention strategy (full model I) and a full model using the type of intervention (full model II).

Printed/digital material was found to be a more effective intervention to improve the outcome measures in model II, with the addition of education and training/group discussion in the full model II. Educational and combined intervention strategies had similar effectiveness on the outcome measure in model III and the full model I.

Studies with a longer period of follow-up were associated with more effective interventions based on both of the full models. Regarding the continent in the full models, overall, studies in five continents reported similar effects on the outcome measures.

Discussion

As diabetes is a global health problem, the studies included in this review comprise all six continents. Asia and America (North and South America) are the biggest contributors to this review with US and India as the two countries with the highest number of studies. A high number of studies from these continents might be related to a higher number of patients with diabetes.[4] Results from other systematic reviews have also shown that more studies are being conducted in the United States (US) on this topic.[20,28,87] This might be due to the high prevalence of diabetes and higher spending on research and development in the US.[88]

As shown by our results, various interventions have been implemented by pharmacists all over the world (see Table 2) to improve medication adherence. Most interventions require the involvement of the patient in the decision making related to his condition, aim to raise awareness about diabetes and aim to improve treatment management, especially medication adherence in achieving optimal treatment targets. There were three studies that involved other health care professionals i.e. a dietician, nurse, nutritionist, or physical therapist during some part of the intervention.[32–34] Several studies indicated that pharmacists also directly collaborated with a physician if approval for medication modification was needed by the patient. This finding emphasizes the importance of collaboration between pharmacists and other health care professionals to provide more comprehensive care for the patient.

Standardized outcome measures (Cohen's d) enable a meta-analysis of studies with different outcome measures, which distinguishes this study from previous systematic reviews. The overall analysis shows that a pharmacist's involvement in patient care enhances outcomes of patients

Table 2
Characteristic of the studies.

Characteristic	No of articles
Region/Country	
Asia	
India[21,35–44]	11
Malaysia[24,45–47]	4
Jordan[48–50]	3
China[51,52]	2
Iran[53,54]	2
Hong Kong[55]	1
Iraq[56]	1
Taiwan[57]	1
Thailand[58]	1
United Arab Emirates[59]	1
North America	
United State of America[32–34,60–72]	16
Canada[73]	1
Europe	
United Kingdom[23,74]	2
Belgium[75]	1
Cyprus[76]	1
Denmark[77]	1
Spain[78]	1
Sweden[79]	1
South America	
Brazil[25,80–82]	4
Africa	
Ethiopia[83]	1
Nigeria[84]	1
Australia[85,86]	2
Age	
Control group	
< 50[37,59,66]	3
50 to 59[21,24,33,35,36,38–45,47,48,50–54,56,58,60,61,68,70–72,83]	29
60 to 65[25,46,55,62,65,67,69,73,75–78,80–82,84,85]	17
≥65[23,32,34,49,57,63,64,74,79,86]	10
Treatment group	
< 50[37,59,66]	3
50 to 59[21,24,32,33,35,36,38–45,47,48,50–54,56,58,60–62,64,68,70–73]	32
60 to 65[25,34,46,49,55,63,65,67,75,76,78,80–85]	18
≥65[23,36,57,74,79,86]	6
Intervention strategy	
Educational intervention[21,36–38,41–45,52,72,84]	12
Behavioral intervention[67]	1
Combined intervention[23–25,32-35,39,40,46-51,53–66,68-71,73–83,85,86]	46
Type of intervention[a]	
Education (disease, medication, lifestyle)[21,24,25,32,34,37,40-42,45–61,63–66,68,69,71–81,83,84]	45
Consultation[21,23,25,35,36,38–40,42–45,50–54,57,60,64,65,69–72,74–78,83,84]	32
Medication review[24,25,33,47,54–57,61,62,64–67,70,71,74,76–78,80–83,85,86]	26
Printed or digital materials[21,23–25,33,35,38–40,42–44,46,49,50,54,59,60,76,79,82,86]	24
Telephone call[23,25,33,39,47,49–52,54,56,57,61,69–71,83–86]	20
Diary/record book[35,39,48,53,54,59,74,79]	8
Training or group discussion[33,52,60,64,68,83]	6
Others (referral, health equipment)[33,47,48,54,57,63,65,74,77,79]	10
Risk of bias	
Some concern[24,25,32,34,37–41,44,45,47–49,51–53,55–59,62,63,66–68,71,73–76,78–81,83,84]	38
High risk[21,23,33,35,36,42,43,46,50,54,60,61,64,65,69,70,72,77,82,85,86]	21

[a] Number of articles might be more than total because there is a possibility of duplication between types of intervention.

with diabetes. The variation in the period of follow-up (1–24 months) that was also found in previous studies (3–24 months)[20,26,28,89] shows that period of follow up depended on the design of the study and type of outcome measure used in the study. Different periods of follow-up had a significant effect on the overall outcome, i.e. ≤ 3 months, > 3 -≤ 6 months and > 6 months. A longer period of follow-up might produce better results (based on the full model) and also could be used to determine the sustainability of the intervention. Three intervention strategies were identified in this study. The combined intervention strategy involving educational and behavioral interventions was the most popular

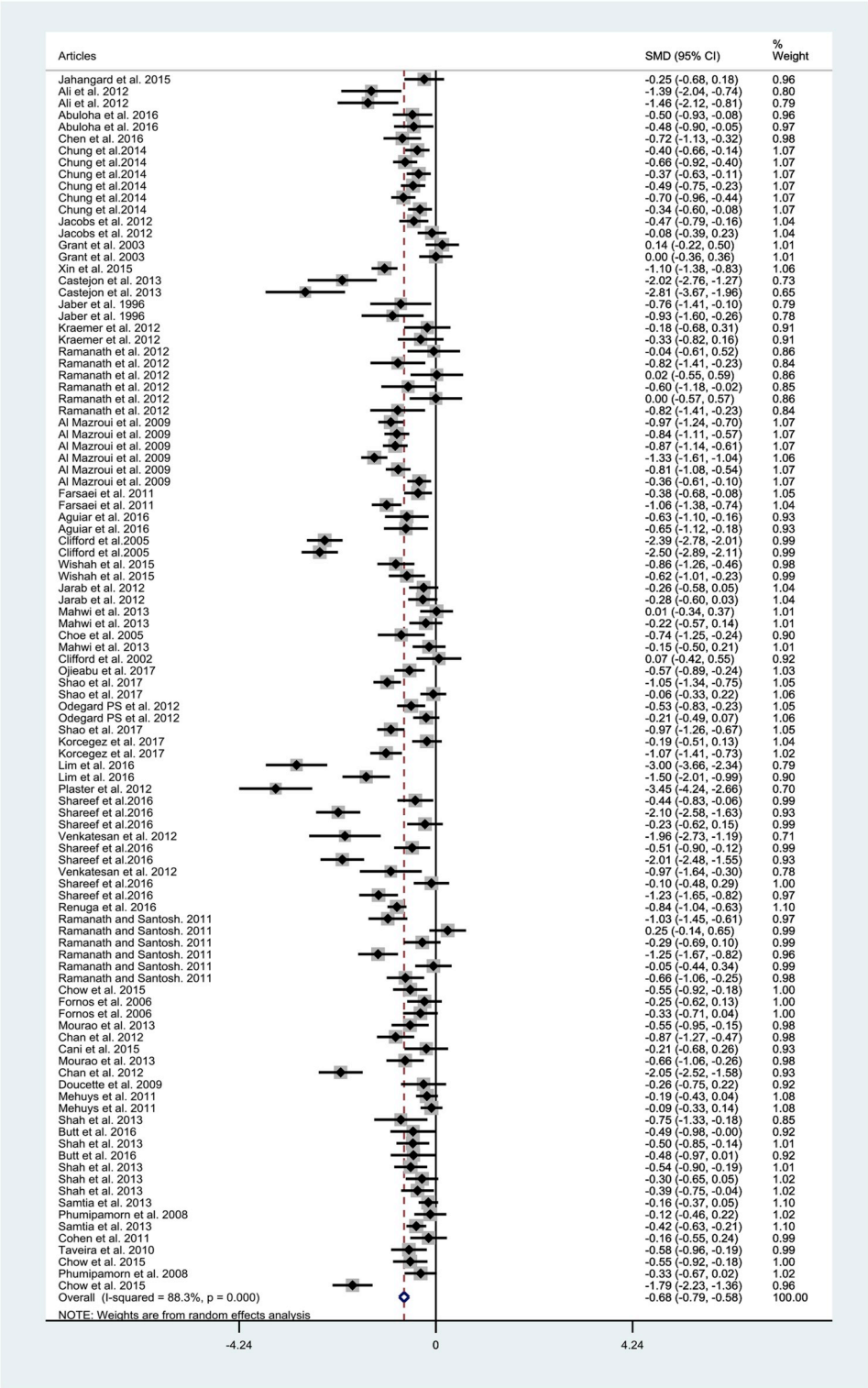

Fig. 2. The overall effect size of all studies included in the analysis.

strategy used by the pharmacist, followed by the educational intervention strategy. This finding is also supported by the fact that education is the most common method used by pharmacists to enhance medication adherence,[21,24,25,32,40,45–55,57–61,63–65,68,69,72,74–81,83,90–96] followed by consultation as the second most common intervention.[21–23,25,38–40,42,44,45,50–54,57,60,64,65,69,70,72,74–78,83,95–98] This finding is in line with results of prior systematic reviews,[20,28,99] especially about the individual type of intervention. This study showed that education was usually integrated into each intervention strategy and is seen as a cornerstone to improve medication adherence by involving the health care professional and the patient.[6,100] The combined educational-behavioral strategy aimed at enhancing the knowledge of patients about diabetes (aetiology, short and long-term complication of diabetes, risk factors of diabetes and complications) and strengthening diabetes management (treatment target monitoring, lifestyle changing behavior, the timing of medication, adverse drug reactions monitoring, and medication adherence) to make them more

Table 3
Effect size per outcome measure based on follow-up period and intervention strategy.

	Detail	Medication adherence	HbA1c	Blood test other than HbA1c (FPG/PPG/RBG)	Total
Period of follow up	**≤3 months**				
	N	10	7	15	32
	D + L pooled SMD	0.577	−0.690	−0.419	−0.524
	CI lower	0.230	−1.147	−0.652	−0.700
	CI upper	0.923	−0.233	−0.186	−0.348
	Heterogeneity (Q)/d.f.	64.84*/9	56.00*/6	70.68*/14	193.49*/31
	I^2	86.10%	89.30%	80.20%	84.00%
	tau squared	0.265	0.330	0.160	0.209
	test of SMD = 0;Z value	3.26*	2.96*	3.53*	5.83*
	> 3-≤6 months				
	N	5	18	16	39
	D + L pooled SMD	0.673	−0.345	−0.889	−0.607
	CI lower	0.296	−0.456	−1.187	−0.752
	CI upper	1.050	−0.234	−0.590	−0.462
	Heterogeneity (Q)/d.f.	22.67*/4	30.24*/17	175.66*/15	258.30*/38
	I^2	82.40%	43.80%	91.50%	85.30%
	tau squared	0.150	0.023	0.324	0.173
	test of SMD = 0; Z value	3.50*	6.10*	5.84*	8.20*
	> 6 months				
	N	4	17	11	32
	D + L pooled SMD	0.874	−0.860	−1.069	−0.927
	CI lower	0.196	−1.120	−1.504	−1.138
	CI upper	1.552	−0.600	−0.634	−0.716
	Heterogeneity (Q)/d.f.	36.75*/3	143.46*/16	160.72*/10	342.00*/32
	I^2	91.80%	88.80%	93.80%	90.90%
	tau squared	0.437	0.258	0.490	0.326
	test of SMD = 0; Z value	2.52*	6.49*	4.81*	8.61*
Intervention strategy	**Educational intervention**				
	N	9	4	12	25
	D + L pooled SMD	0.591	−0.695	−0.655	−0.636
	CI lower	0.342	−1.089	−0.993	−0.827
	CI upper	0.841	−0.302	−0.317	−0.446
	Heterogeneity (Q)/d.f.	29.71*/8	15.15*/3	130.12*/11	176.15*/24
	I^2	73.10%	80.20%	91.50%	86.40%
	tau squared	0.106	0.122	0.320	0.197
	test of SMD = 0: Z value	4.64*	3.46*	3.80*	6.55*
	Combined intervention (Educational + behavioral)				
	N	10	38	30	78
	D + L pooled SMD	0.729	−0.610	−0.818	−0.702
	CI lower	0.332	−0.774	−1.040	−0.827
	CI upper	1.125	−0.447	−0.595	−0.577
	Heterogeneity (Q)/d.f.	96.57*/9	287.74*/37	302.06*/29	692.38*/77
	I^2	90.70%	87.10%	90.40%	88.90%
	tau squared	0.363	0.222	0.331	0.271
	test of SMD = 0: Z value	3.60*	7.32*	7.20*	10.98*
TOTAL	N	19	42	42	103
	D + L pooled SMD	0.663	−0.617	−0.768	−0.684
	CI lower	0.429	−0.767	−0.951	−0.789
	CI upper	0.898	−0.467	−0.585	−0.580
	Heterogeneity (Q)/d.f.	127.12*/18	304.74*/41	434.18*/41	868.62*/102
	I^2	85.80%	86.50%	90.60%	88.30%
	tau squared	0.229	0.205	0.316	0.249
	test of SMD = 0; Z value	5.54*	8.05*	8.23*	12.82*

*p < 0.05; FPG = fasting plasma glucose; PPG = post-prandial blood glucose; RBG = random blood glucose; SMD = standardized mean difference; CI = confidence interval; d.f = degree of freedom, see Appendix 4 and 5 for the forest plot result.

aware of their condition and to change their behavior to achieve better outcomes.[101] Both strategies (the educational and the combined educational-behavioral strategy) are effective in improving medication adherence and glycemic goals. Subgroup analysis of the individual types of interventions, specifically education and consultation, showed a significant improvement on the overall glycemic goal and medication adherence. Therefore, this study does not conclude that these two types of individual interventions are the best methods to overcome non-adherence because the effectiveness of this strategy is not consistent among all studies. Further analysis based on the meta-regression showed that compared with a telephone call, education is more effective, and consultation is as effective as a telephone call. A non-significant result was detected in 11 studies.[58,60,63,65,68,69,72,75,76,80,90] Some factors that might influence the inconsistent results between studies are the adherence level at baseline of the sample, which in most cases is already high[63]; small sample size and shorter duration of the intervention[60]; an unbalanced baseline between groups[58]; and better baseline values of glycemic outcome nearing the treatment target (90–140 mg/dL). These make it harder to enhance outcomes compared with patients with poor baseline values.[68,75] The effectiveness of education has also been shown in prior systematic reviews,

Table 4
Result of meta-regression analysis – the association of study characteristic with effect size measures (103 observations).

Characteristic	Coefficient	Standard error	Lower 95% CI	Upper 95% CI
Model I (Outcome measures)				
Outcome measures				
HbA1c (reference category)				
Medication adherence	−0.040	0.185	−0.407	0.328
Blood test other than HbA1c (FPG/PPG/RBG)	−0.147	0.147	−0.438	0.144
Constant	−0.626*	0.103	−0.831	−0.421
tauˆ2 = 0.3747				
Model II (Type of intervention)				
Types of intervention				
Telephone call (reference category)				
Education (disease, medication, lifestyle)	−0.111	0.219	−0.547	0.325
Consultation	0.096	0.165	−0.232	0.423
Medication review	−0.332	0.200	−0.729	0.064
Printed or digital material	−0.538*	0.191	−0.917	−0.159
Diary record book	0.027	0.187	−0.343	0.398
Training or group discussion (medication)	−0.508	0.290	−1.083	0.068
Others (referral, health equipment)	0.176	0.271	−0.363	0.715
Total combination	−0.004	0.110	−0.223	0.215
Constant	−0.297	0.227	−0.747	0.153
tauˆ2 = 0.3155				
Model III (Intervention strategy)				
Intervention strategy				
Educational intervention (reference category)				
Combined intervention	−0.007	0.160	−0.324	0.310
Total combination	−0.075	0.057	−0.189	0.038
Constant	−0.464*	0.189	−0.839	−0.089
tauˆ2 = 0.3706				
Model IV (Continent)				
Continent				
Asia (reference category)				
North America	0.152	0.166	−0.179	0.482
Europe	0.109	0.245	−0.379	0.596
South America	−0.243	0.287	−0.812	0.326
Australia	−0.949*	0.388	−1.719	−0.180
Africa	0.123	0.646	−1.160	1.405
Constant	−0.690*	0.082	−0.852	−0.528
tauˆ2 = 0.3473				
Model V (Other characteristics)				
Follow-up period (months)	−0.059*	0.016	−0.092	−0.027
Sample size	0.001	0.001	−0.001	0.002
Age of treatment group (years)	−0.022	0.088	−0.196	0.152
Year of publication	0.018	0.016	−0.014	0.050
Risk of bias (high)	−0.336*	0.140	−0.613	−0.059
Constant	−0.297	0.292	−0.877	0.284
tauˆ2 = 0.3172				
Full Model (I)				
Outcome measures				
HbA1c (reference category)				
Medication adherence	−0.139	0.191	−0.518	0.239
Blood test other than HbA1c (FPG/PPG/RBG)	−0.198	0.147	−0.491	0.094
Intervention strategy				
Educational intervention (reference category)				
Combined intervention	−0.030	0.203	−0.435	0.374
Total combination	−0.020	0.060	−0.139	0.100
Continent				
Asia (reference category)				
North America	0.265	0.205	−0.142	0.672
Europe	0.352	0.296	−0.235	0.940
South America	−0.044	0.307	−0.655	0.567
Australia	−0.603	0.503	−1.602	0.396
Africa	0.102	0.669	−1.227	1.431
Follow-up period	−0.063*	0.018	−0.099	−0.027
Sample size	0.001	0.001	−0.001	0.003

(*continued on next page*)

Table 4 (*continued*)

Characteristic	Coefficient	Standard error	Lower 95% CI	Upper 95% CI
Age of treatment group	−0.044	0.121	−0.285	0.197
Year of publication	0.015	0.021	−0.027	0.057
Risk of bias (high)	−0.272	0.178	−0.627	0.082
Constant	−0.135	0.404	−0.937	0.667
tau^2 = 0.3047				
Full Model (1I)				
Outcome measures				
HbA1c (reference category)				
Medication adherence	−0.306	0.186	−0.676	0.063
Blood test other than HbA1c (FPG/PPG/RBG)	−0.141	0.140	−0.420	0.138
Type of intervention				
Telephone call (reference category)				
Education (disease, medication, lifestyle)	−0.554*	0.270	−1.092	−0.016
Consultation	−0.137	0.226	−0.588	0.313
Medication review	−0.508	0.283	−1.071	0.054
Printed or digital material	−0.613*	0.217	−1.045	−0.181
Diary record book	−0.403	0.218	−0.836	0.030
Training or group discussion (medication)	−1.152*	0.363	−1.875	−0.429
Others (referral, health equipment)	−0.214	0.293	−0.797	0.368
Total combination	0.239	0.135	−0.029	0.507
Continent				
Asia (reference category)				
North America	0.396	0.238	−0.078	0.870
Europe	0.589	0.351	−0.108	1.287
South America	0.269	0.331	−0.390	0.928
Australia	−0.648	0.495	−1.634	0.337
Africa	−0.344	0.636	−1.608	0.921
Follow-up period	−0.047*	0.019	−0.085	−0.009
Sample size	−0.001	0.001	−0.002	0.001
Age of treatment group	−0.242	0.122	−0.484	< -0.001
Year of publication	0.028	0.021	−0.013	0.069
Risk of bias (high)	−0.234	0.198	−0.629	0.161
Constant	0.645	0.475	−0.300	1.590
tau^2 = 0.2627				

*p < 0.05.

even though not all studies have had a large sample size.[27] The quality and sustainability of education also needs to be considered and associated with the patient's need to produce a long-term effect, instead of a short-term effect only.

Medication review is the third most common method found in this systematic review.[24,25,33,47,51,54,55,57,61,62,64,65,67,70,74,76–78,80,81,83,85,86,91,92,95,96,102] This type of individual intervention is based on an intervention strategy that combines educational and behavioral elements. This is because patients not only get information related to the problem found during the review but also need to change or modify their behavior to achieve treatment goals and improve medication adherence. Together with education and consultation, medication review also has a significant effect on the overall outcome measures (stated medication adherence, HbA1c, blood test other than HbA1c (FPG, PPG, RBG)). Even though there were significant effects detected for all types of interventions, a comparison of effectiveness between them showed that education, printed or digital material, and training or group discussion are more effective to improve outcomes compared with a telephone call (see Table 4). The effectiveness of medication review along with education and consultation in the analysis to improve glycemic outcomes and stated medication adherence, indicate the evolving role of the pharmacist to support patient care in collaboration with other health care professionals. It also indicates that pharmacists do not replace the function/role of other healthcare professionals. This was also supported by some studies included in this review, which reported that the pharmacist always contacted the patient's physician for approval if any medication modification were made during the intervention.[23–25,33,47–50,54–57,59,61,62,64–67,70,71,74,76–83,85,86]

Further study is needed to explore the factors to effectively implement this method and strategy such as the willingness of the pharmacist to collaborate and the clinical skills and access to resources needed to do the medication review and the recognition of the pharmacist's role by the physician.[103] Further analysis of the differences in effectiveness between studies across continents is also needed.

The quality assessment of the reviewed publications using the Cochrane tool (RoB.2) might have been influenced by under-reported information, for example information related to allocation concealment and blinding between groups, which was often absent. Further analysis also showed that publication bias might have affected the results of this study, even though the meta-regression analysis of the full models showed no significant association between the risk of bias and the effectiveness of the intervention. Above all, this review showed effective and significant improvement of the outcome measure including stated medication adherence by the different pharmacist's interventions.

This review has several limitations that need to be acknowledged other than the limitation in quality assessment and publication bias that might have affected the results. First, there were several studies for which the effect size could not be calculated and analyzed because of the lack of information provided by the study, e.g. missing mean and SD values. Second, most of the studies showed a significant improvement because of medication adherence, but one thing that should be kept in mind is that the stated medication adherence was based on a self-reported measurement and this may have biased the results. Third, there were a limited number of studies for a certain outcome measure, especially PPG and RBG, which may have under or overpowered the results. Finally, based on the analysis, one of the limitations of this study was the difficulty to choose the best strategy to improve medication adherence in a patient with diabetes because most of the interventions used in this review were a combination of interventions. Only 8 studies used a single intervention.

Conclusion

This systematic review provides evidence on the role of pharmacy in diabetes care around the world to enhance and improve medication adherence and blood glucose control among patients with diabetes. The effectiveness of pharmacy-related interventions was determined by the overall and sub-analysis of the effect size for three types of outcome measure (stated medication adherence, HbA1c, blood test other than HbA1c (FPG, PPG, RBG)). This finding also supports a potential role of the pharmacist in diabetes care to help and support other healthcare professionals to achieve optimal treatment targets, especially in improving medication adherence among patients with diabetes. Further studies are needed to explore the feasibility, and barriers to implementing the interventions in different population groups.

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Conflicts of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sapharm.2018.09.021.

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