Elsevier Editorial System(tm) for Value in Health
Manuscript Draft

Manuscript Number: VIH-2014-397R1

Title: Effectiveness and content analysis of interventions to enhance oral antidiabetic drug adherence in adults with type 2 diabetes: Systematic review and meta-analysis

Article Type: Systematic Review

Keywords: adherence,
psychosocial intervention,
oral antidiabetic drug,
diabetes,
Meta-analysis

Corresponding Author: Dr. Line Guénette, Ph.D.

Corresponding Author's Institution: Université Laval

First Author: Hervé Tchala Vignon Zomahoun, PhD candidate

Order of Authors: Hervé Tchala Vignon Zomahoun, PhD candidate; Marijn de Bruin, PhD; Laurence Guillaumie, PhD; Jocelyne Moisan, PhD; Jean-Pierre Grégoire, PhD; Norma Pérez, MSc; Lydi-Anne Vézina-Im, PhD candidate; Line Guénette, PhD

Abstract: Objectives: To estimate the pooled effect size of oral antidiabetic drug (OAD) adherence-enhancing interventions, and to explore which of the behavior change techniques (BCTs) that were applied in the intervention groups modified this pooled intervention effect size.
Methods: We searched relevant studies published until 3 September 2013 on Medline, Embase, PsycInfo, the Cochrane Library, CINAHL, Current Contents Connect, and Web of Science. Selected studies were qualitatively synthesized, and those of at least medium quality were included in the meta-analysis. A random-effects model was used to pool effectiveness (Hedges's g) and to examine heterogeneity (Higgins I^2). We also explored the influence on the pooled effectiveness of unique intervention BCTs (those delivered to the intervention but not control groups in a trial) by estimating their modifying effects.
Results: Fourteen studies were selected for the qualitative synthesis and 10 were included in the meta-analysis. The pooled effectiveness of the interventions was 0.21 (95% CI=-0.05-0.47; I^2=82%). Eight unique BCTs were analyzed. "Cope with side effects" (p-value=0.003) and "general intention formation" (p-value=0.006) had a modifying effect on the pooled effectiveness. The pooled effectiveness of the interventions in which "cope with side effects" was applied was moderate (0.64; 95% CI=0.31-0.96; I^2=56%).
Conclusions: Overall effectiveness of OAD adherence-enhancing interventions that have been tested is small. Helping patients cope with side effects or formulate desired treatment outcomes could impact the effectiveness of OAD adherence-enhancing interventions. However, only interventions that include helping patients to cope with side effects appear to be particularly effective in improving OAD adherence.

Suggested Reviewers:

Response to Reviewers: We thank you for this opportunity to send a revised version of our manuscript. We have enclosed a point-by-point detailed response to the comments (in addition to the following section) and a revised marked copy (we have used the MS Word "track changes" function) showing changes in the manuscript.

Reviewer #1:

Response to comment No. 1: Hedges's g was used for both continuous and dichotomous adherence variables. They were directly computed based on adherence continuous measures reported in 5 studies. However, for the five studies in which adherence was measured on a dichotomous scale, odds ratios had first to be transformed into Cohen's d from which they were then transformed into Hedges's g (SMD). To make it clearer we have modified a paragraph in the data synthesis and analysis section.

Response to comment No. 2: We thank the reviewer for pointing this out. We agree that the decision to use a fixed-effects or a random-effects model should not be based on empirical heterogeneity but on prior assumptions. In the taxonomy of behaviour change, there are many BCTs (Michie, 2008; Marijn, 2010). We then anticipated that there would be a wide array of different BCTs applied in behavioural interventions and expected a-priori high heterogeneity that was later empirically confirmed. We have therefore added sentences in the data synthesis and analysis section.

Response to comment No. 3: We thank the reviewer for this relevant point. We now report this limitation in the section on strengths and limitations.

Response to comment No. 4: We used the adherence categorization as reported in the articles. To make it clearer, in the results section on pooled intervention effect on OAD adherence, we added some information.

Response to comment No. 5: We agree with the reviewer that MPR > 100% could be of concern. MPR was used in two of the studies included in our meta-analysis (Odegard, 2012; Walker, 2011). In one (Odegard, 2012) of those, the authors reported that the MPR value was capped at 100%. In the other study, the authors neither mentioned if MPRs could be greater than 100%, nor how they eventually handled these cases (Walker, 2011). However, based on our sensitivity analyses, excluding those two studies had no effect on the pooled intervention effect size estimate. As suggested, we are now discussing this concern in the section on strengths and limitations.

Response to comment No. 6: In our preliminary analyses, we explored the influence of some factors, including duration of intervention period, on the pooled intervention effect size. None of those factors had an influence on the pooled intervention effect size (see table below). This information was not included in our manuscript in order to keep the focus on the BCTs analyses in support of the main objective of our study. However, we agree this information is of interest. We are now reporting this information as an online supplementary material table (Supplementary-Table S7).

Responses to comment No. 7: We agree with the reviewer that the exploration of these variables is of interest. As stated above in our response to comment no 6, we have conducted subgroup analyses. The results are now reported in the online supplementary table S7.

Response to comment No. 8: We agree with the reviewer that people with psychiatric comorbidities such as depression are less likely than others to comply with drug treatment. As only randomized controlled trials were included in our meta-analysis, one can expect patients' comorbidities to be equally distributed in both the intervention and control groups. To address this concern, we have added some text in the "Strengths and limitations" section

Response to comment No. 9: We thank the reviewer for pointing this out. We have deleted the parts that were already included in the discussion section.

Reviewer #2:

Response to comment No. 10: Yes, they were all included. Since in each of the 10 articles there was only one intervention studied for which it was possible to estimate the effect size on oral antidiabetic drug adherence, the number of studied interventions totalled 10. To clarify this point, we have added two sentences.

Response to comment No. 11: We understand the reviewer's concern about the coding procedure. Indeed, at first when we saw this rather counterintuitive result, we did have another look at the articles and checked for accuracy both the coding process and the statistical analyses. Those were indeed accurate. That being said, when looking at the components of the interventions more closely, we observed that the BCT "cope with side effects" was only applied in studies in which the BCT "general intention formation" was not, i.e., in those studies included in the comparison group for "general intention formation". Since "cope with side effects" is effective in enhancing OAD adherence, it might explain why the "general intention formation" group did worst than the group in which "general intention formation" was not applied (yet "cope with side effects" was). We have modified this section for more clarity.

Response to comment No. 12: We chose not to include the protocol in the online appendix since it would be repetitive of the method section. Instead, we are providing very detailed online supplementary material that should allow any reader to reproduce our study: detailed search strategies for each database consulted (supplementary Table S1); data collection form (supplementary Table S2); assessment tool of intervention study methodological quality (supplementary Table S2); and coding manual of behavior change techniques (supplementary Table S3).

Reviewer #3:

Response to all comments: We thank the reviewer for these very positive comments.

*Cover Letter

UNIVERSITÉ LAVAL

Faculté de pharmacie

Pavillon Ferdinand-Vandry
1050, avenue de la Médecine
Québec (Québec) G1V 0A6
CANADA

418 656-3211
Télécopieur : 418 656-2305
www.pha.ulaval.ca

Quebec, December 22, 2014

Dr. Alex Z. Fu
Co-Editor, Value in Health

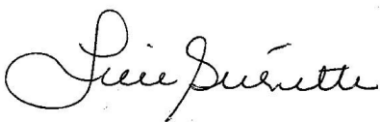
Object: Revised submission of the article "Effectiveness and content analysis of interventions to enhance oral antidiabetic drug adherence in adults with type 2 diabetes: Systematic review and meta-analysis"

Dear Dr. Fu,

We thank you for this opportunity to send a revised version of our manuscript. We thank the editor and reviewers for their comments and suggestions. We believe the quality of our manuscript has improved through this process. We have enclosed a point-by-point detailed response to the comments, a revised marked copy (we have used the MS Word "track changes" function) showing changes in the manuscript and a clean copy of the manuscript and of the supplementary files.

We sincerely hope our manuscript is now suitable for publication in your journal. We look forward to hearing from you in the near future.

Best regards,



Line Guénette, BPharm, MSc, PhD
Assistant Professor, Faculty of Pharmacy, Laval University
Researcher, Centre de recherche du CHU de Québec
Axe Santé des populations et pratiques optimales en santé
1050 Chemin Ste-Foy
Québec, QC, Canada, G1S 4L8
Telephone: 418-682-7511 # 4694, Fax: 418-682-7962

RESPONSES TO COMMENTS

We thank you for this opportunity to send a revised version of our manuscript. We thank the editor and reviewers for their comments and suggestions. We believe the quality of our manuscript has improved through this process. We have enclosed a point-by-point detailed response to the comments and a revised marked copy (we have used the MS Word "track changes" function) showing changes in the manuscript.

Reviewer #1:

I have only a few comments which are as follows:

1. P5: Why were dichotomous adherence variables eventually transformed into Cohen's d rather than Hedge's g? If I understand correctly, Hedge's g was used for continuous variables.

Response: Hedges's g was used for both continuous and dichotomous adherence variables. They were directly computed based on adherence continuous measures reported in 5 studies. However, for the five studies in which adherence was measured on a dichotomous scale, odds ratios had first to be transformed into Cohen's d from which they were then transformed into Hedges's g (SMD). To make it clearer we have modified the following paragraph in the data synthesis and analysis section (additions are in italics).

> "*When adherence was reported on a continuous scale, we directly computed Hedges's g based on sample sizes and adherence means of both intervention and control groups.* In order to be able to pool studies in which OAD adherence was reported as a binary variable with those in which it was reported as a continuous variable, we made the following transformation for OAD adherence binary variables. We calculated the odds ratio (OR), converted it to Cohen's d using the formula $d = 3^{1/2} \ln(OR)/ \pi$ (24, 25), *which was then transformed into* SMD (*Hedges's g)* = [(1–3/(4N1 + 4N2 – 9))*d] with N1= intervention group sample size and N2= control group sample size.(24)."

2. P5: „…we planned to first conduct a fixed-effects meta-analysis and to turn it into a random-effects model if heterogeneity was high". The decision of fixed vs. random effects should not be based on empirical heterogeneity but on whether or not the assumption holds that all studies are logically related/ logically equivalent. If studies are suspected to be different from their basis (e.g. population characteristics that may influence the main effects beyond mere sampling error) one should consider random effects pooling [cp. Borenstein et al. Introduction to Meta-Analysis. Chichester, UK: Wiley: 2009].

Response: We thank the reviewer for pointing this out. We agree that the decision to use a fixed-effects or a random-effects model should not be based on empirical heterogeneity but on prior assumptions. In the taxonomy of behaviour change, there are many BCTs (Michie, 2008; Marijn, 2010). We then anticipated that there would be a wide array of different BCTs applied in behavioural interventions and expected a-priori high heterogeneity that was later empirically confirmed. We have therefore added the following sentences (italics) in the data synthesis and analysis section.

> *"Our review focused on a wide variety of behavioural interventions aiming to enhance oral antidiabetic drug adherence. Therefore, we anticipated there would be heterogeneity in the estimate of the pooled intervention effect size. In order to take into account this potential heterogeneity, random-effects model was used to estimate the pooled intervention effect size and its 95% interval confidence (CI)* (26). Pooled SMD values of < 0.2, ≥ 0.2 to <0.5, ≥ 0.5 to < 0.8, or ≥ 0.8 were considered very small, small, medium and large, respectively (27)."

3. Adherence studies usually face the problem that one does not know to what extent the magnitude of patient adherence translates into meaningful clinical outcomes. Although the authors say that BCTs have a small effect on adherence, this does not necessarily preclude positive/negative effects on patient health. The authors also refer to SMDs as small, medium, or large as suggested by Cohen. This could be misleading as there is no justification for the clinical/practical significance of such effect differences for patient health. I think this should at least be mentioned briefly in the limitations section. In case there were widely accepted adherence thresholds in OAD treatment, the authors might consider using risk ratios instead of standardized differences since these are more intuitive.

Response: We thank the reviewer for this relevant point. We now report this limitation in the section on strengths and limitations.

> *"First, we classified SMDs as small, medium or large as suggested by Cohen. However, when interpreting these SMDs, one should be aware that the clinical significance of such effect size for patient health is unclear."*

4. If studies used adherence categories, was the same cut-off value used to discriminate between these categories (e.g. adherents / non-adherents)?

Response: We used the adherence categorization as reported in the articles. To make it clearer, in the results section on pooled intervention effect on OAD adherence, we added the following information.

> "Intervention effects on OAD adherence were both positive and statistically significant (P< 0.05) in six studies (36, 39, 41, 44, 46, 47), null in four studies (37, 38, 43, 45), and negative in one study (40). A total of 10 studies were included in the meta-analysis because the intervention effect size could not be calculated for one study (44). *Adherence was either measured on a dichotomous (36, 41, 43, 45, 46) or continuous scale (37, 38, 39, 40, 47). When the reported adherence measure was dichotomous, we used the categorization cut-off value as reported in the study articles."*

5. Depending on the type of measure used, adherence values may exceed 100% (e.g. when medication possession ratios are calculated). This means that in extreme cases adherence may rise from 100% to - say - 120% following intervention. This, of course, would be irrelevant from a clinical perspective and should then be discussed (or excluded from the analysis).

Response: We agree with the reviewer that MPR > 100% could be of concern. MPR was used in two of the studies included in our meta-analysis (Odegard, 2012; Walker, 2011). In one (Odegard, 2012) of those, the authors reported that the MPR value was capped at 100%. In the other study, the authors neither mentioned if MPRs could be greater than 100%, nor how they eventually handled these cases (Walker, 2011). However, based on our sensitivity analyses, excluding those two studies had no effect on the pooled intervention effect size estimate. As suggested, we are now discussing this concern in the section on strengths and limitations.

> "*The MPR was used to measure adherence in two studies (39, 46). Since the MPR can in theory be greater than 100%, including studies using the MPR could have inflated to some extent the effect size in a clinically non-relevant way. Although the authors of one study (46) did not mention how they handled cases of MPR greater than 100%, in the other study (39) the MPR was capped at 100%. Moreover, in our sensitivity analyses, excluding the effect size from those two studies had no impact on the pooled intervention effect size estimate*. "

6. It would be interesting to see whether the duration of follow-up has an impact on adherence.

Response: In our preliminary analyses, we explored the influence of some factors, including duration of intervention period, on the pooled intervention effect size. None of those factors had an influence on the pooled intervention effect size (see table below). This information was not included in our manuscript in order to keep the focus on the BCTs analyses in support of the main objective of our study. However, we agree this information is of interest. We are now reporting this information as an online supplementary material table (Supplementary-Table S_7).

Supplementary-Table S_7: Impact of studies characteristics on pooled intervention effect size

Characteristics	N	Random-effects models			
		Hedges's g	95%CI	*p*-value	I^2
Mean age of participants					
≥ 60 years	4	0.17	-0.25 – 0.59		85%
< 60 years	6	0.24	-0.13 – 0.60		83%
Test for subgroup differences:				0.820	----
Type of OAD adherence measure					
subjective (self-report)	4	-0.03	-0.42 – 0.37		78%
objective (electronic or database)	6	0.36	0.07 – 0.64		76%
Test for subgroup differences:				0.130	----
Importance of OAD adherence as an outcome					
primary outcome	6	0.40	0.04 – 0.77		80%
secondary outcome	4	-0.04	-0.35 – 0.27		75%
Test for subgroup differences:				0.070	----
OAD adherence scale					
dichotomous	5	0.32	-0.10 – 0.74		85%
continuous	5	0.11	-0.25 – 0.47		82%
Test for subgroup differences:				0.470	----
Use of an intervention guide					
yes	6	0.31	-0.03 – 0.65		86%
no	4	0.04	-0.39 – 0.47		76%
Test for subgroup differences:				0.330	----
Duration of intervention period					
≥ 6 months	5	0.10	-0.16 – 0.37		72%
< 6 months	5	0.36	-0.19 – 0.92		89%
Test for subgroup differences:				0.410	----

N= number of studies; Hedge's g= bias-corrected standardized mean difference; CI= confidence interval; I^2= indicator of heterogeneity; OAD= oral antidiabetic drug

7. This relates to comment 4, 5, and 6: One could test the impact of potential effect modifiers such as type of adherence measure, duration of follow-up, population age and sex, etc. in a meta-regression framework. If the limited number of trials is a concern, the authors could conduct a subgroup analysis for these factors (similar to what they did for different BCTs).

Responses: We agree with the reviewer that the exploration of these variables is of interest. As stated above in our response to comment no 6, we have conducted subgroup analyses. The results are now reported in the online supplementary table S_7.

8. Were there any subjects with psychiatric comorbidities in the studies reviewed? These populations are less likely to comply with drug treatment and may thus bias findings.

Response: We agree with the reviewer that people with psychiatric comorbidities such as depression are less likely than others to comply with drug treatment. As only randomized controlled trials were included in our meta-analysis, one can expect patients' comorbidities to be equally distributed in both the intervention and control groups.

To address this concern, we have added the following (added text is in italics) in the "Strengths and limitations" section

> *"...* Two independent coders conducted all of the coding, and we selected only quality studies for the meta-analyses. *Moreover, all studies included in our meta-analysis were RCTs. Therefore, one could expect some patient's characteristics that are likely to be associated with medication adherence (e.g. depression) would be equally distributed in the intervention and control groups.*"

9. Please revise the conclusion section since parts of it rather belong in the discussion (only sentences no. 3, 5 and 6 contain actual conclusions).

Response: We thank the reviewer for pointing this out. We have deleted the parts that were already included in the discussion section. The conclusion now reads as follow:

> "Behavior change interventions seem to have a small, favorable effect on adherence to OAD treatment. Interventions that include helping people cope with their side effects could be particularly effective in improving adherence to OAD treatment, and we recommend including this in OAD adherence-enhancing interventions. Future studies with better-designed and better-reported interventions are required to identify other behavior change techniques that could benefit patients. *Researchers should also make efforts to better capture the content of usual care at the moment behavioral change interventions are offered."*

Reviewer #2:

General comments

The benefits of Adherence to antidiabetic treatments have been well studied and published. Poor adherence jeopardized the treatment effects and increased the risks of complications. The study systematically assessed health care interventions that help

10. For the pooled effectiveness, what behavioral interventions have been included? Does this mean all the studied interventions from the 10 meta-analyzed articles? Please clarify.

Response: Yes, they were all included. Since in each of the 10 articles there was only one intervention studied for which it was possible to estimate the effect size on oral antidiabetic drug adherence, the number of studied interventions totalled 10. To clarify this point, we have added two sentences.

> "*In each of the 10 study articles there was only one intervention for which it was possible to estimate the effect size on OAD adherence. We pooled the effect sizes of these 10 behavioral interventions in our meta-analysis.* Since the heterogeneity was high (I^2= 82%; (*p*-value< 0.001), we only reported the results of random-effects model (see Figure 2)."

11. For the negative effectiveness of "general intention formation", it does not make sense. I would go back to the 3 articles and also double check the coding.

Response: We understand the reviewer's concern about the coding procedure. Indeed, at first when we saw this rather counterintuitive result, we did have another look at the articles and checked for accuracy both the coding process and the statistical analyses. Those were indeed accurate. That being said, when looking at the components of the interventions more closely, we observed that the BCT "cope with side effects" was only applied in studies in which the BCT "general intention formation" was not, i.e., in those studies included in the comparison group for "general intention formation". Since "cope with side effects" is effective in enhancing OAD adherence, it might explain why the "general intention formation" group did

worst than the group in which "general intention formation" was not applied (yet "cope with side effects" was). We have modified this section for more clarity.

> "Moreover, the BCT "cope with side effects" was only applied in the studies that did not apply the BCT "general intention formation*", those latter studies being the comparison group for the BCT "general intention formation." Therefore, our observation of a decrease in adherence when the BCT "general intention formation" is applied might be due to the fact that this BCT was indirectly compared to BCT "cope with side effects" this latter being effective at enhancing OAD adherence*.

12. **According to PRISMA, it would be valuable to include the study protocol in the online appendix.**

Response: We chose not to include the protocol in the online appendix since it would be repetitive of the method section. Instead, we are providing very detailed online supplementary material that should allow any reader to reproduce our study: detailed search strategies for each database consulted (supplementary Table S1); data collection form (supplementary Table S2); assessment tool of intervention study methodological quality (supplementary Table S2); and coding manual of behavior change techniques (supplementary Table S3).

Reviewer #3: The topic is old, but actual! People do not adhere 100% medication. We continue to ask, why?

Introduction

It's ok

Methods

The present study was performed according to the guidelines of PRISMA. It´s correct in all items!

Results

The authors chose to use the funnel plot and not the forest plot. This is possible because there are 10 studies included!

Discussion/Conclusion

The discussion and conclusion explain how the research has moved the scientific knowledge.

And in the end the problem continue" Future studies with better-designed and better-reported interventions are required".

Response: We thank the reviewer for these very positive comments.

***Key Points**

KEY POINTS:
What is already known on this topic? Many adults who require oral antidiabetic drugs (OADs) do not adhere to their prescribed regimens. Little is known about the overall effectiveness of OAD adherence-enhancing interventions in adults with type 2 diabetes or their active components.
What does the paper add to existing knowledge? Our study suggests that overall effectiveness of OAD adherence-enhancing interventions that have been tested is small. The interventions that include helping patients to cope with side effects appear to be particularly effective in improving OAD adherence. These findings could help health care professionals (physicians, pharmacists, nurses, and health educators) implement effective interventions in their practice to enhance medication adherence among their patients.

***Title Page [including author details]**

Title: Effectiveness and content analysis of interventions to enhance oral antidiabetic drug adherence in adults with type 2 diabetes: Systematic review and meta-analysis

Author names: Hervé Tchala Vignon Zomahoun, Marijn de Bruin, Laurence Guillaumie, Jocelyne Moisan, Jean-Pierre Grégoire, Norma Pérez, Lydi-Anne Vézina-Im, Line Guénette

Academic degrees and affiliations of authors:
Laval University, 1050, avenue de la Médecine Québec (Québec), G1V 0A6 Canada,
Hervé Tchala Vignon Zomahoun PhD candidate, Faculty of pharmacy,
Laurence Guillaumie PhD, Assistant Professor, Faculty of Nursing,
Jocelyne Moisan PhD, Full Professor, Faculty of pharmacy,
Jean-Pierre Grégoire PhD, Full Professor, Faculty of pharmacy,
Lydi-Anne Vézina-Im PhD candidate, Faculty of Nursing,
Line Guénette PhD, Assistant Professor, Faculty of pharmacy,
Centre de recherche du CHU de Québec, Axe Santé des populations et pratiques optimales en santé and Chair on adherence to treatments, 1050 chemin Ste-Foy, Québec, Québec, G1S 4L8 Canada,
Hervé Tchala Vignon Zomahoun,
Laurence Guillaumie,
Jocelyne Moisan,
Jean-Pierre Grégoire,
Line Guénette,
Norma Pérez, MSc, Research Assistant
University of Aberdeen, Institute of Applied Health Sciences, Foresterhill, AB25 2ZD, Scotland,
Marijn de Bruin PhD, Professor Health Psychology.

Corresponding author:
Line Guénette, BPharm, PhD
Assistant Professor, Faculty of Pharmacy, Laval University
Centre de recherche du CHU de Québec, Axe Santé des populations et pratiques optimales en santé, Hôpital du St-Sacrement
1050 Chemin Ste-Foy, Québec, QC, Canada, G1S 4L8
Telephone: 418-682-7511 # 4694, Fax: 418-682-7962
Email: line.guenette@pha.ulaval.ca

Funding: This study was funded by the Laval University Chair on Adherence to Treatments. This Chair is supported by non-restricted grants from AstraZeneca Canada, Merck Canada, Sanofi Canada, Pfizer Canada, and from the *Prends soin de toi program* (a Quebec provincial program for the improvement of public health).

Key words: Adherence, psychosocial intervention, oral antidiabetic drug, diabetes, meta-analysis

Running title: Oral antidiabetic drug adherence intervention

Acknowledgments: We thank Frederic Bergeron, information scientist, for assistance in search strategies. We thank American Journal Experts for editing the text.

ABSTRACT

Objectives: To estimate the pooled effect size of oral antidiabetic drug (OAD) adherence-enhancing interventions, and to explore which of the behavior change techniques (BCTs) that were applied in the intervention groups modified this pooled intervention effect size.

Methods: We searched relevant studies published until 3 September 2013 on Medline, Embase, PsycInfo, the Cochrane Library, CINAHL, Current Contents Connect, and Web of Science. Selected studies were qualitatively synthesized, and those of at least medium quality were included in the meta-analysis. A random-effects model was used to pool effectiveness (Hedges's g) and to examine heterogeneity (Higgins I^2). We also explored the influence on the pooled effectiveness of unique intervention BCTs (those delivered to the intervention but not control groups in a trial) by estimating their modifying effects.

Results: Fourteen studies were selected for the qualitative synthesis and 10 were included in the meta-analysis. The pooled effectiveness of the interventions was 0.21 (95% CI=-0.05–0.47; I^2=82%). Eight unique BCTs were analyzed. "Cope with side effects" (p-value=0.003) and "general intention formation" (p-value=0.006) had a modifying effect on the pooled effectiveness. The pooled effectiveness of the interventions in which "cope with side effects" was applied was moderate (0.64; 95% CI=0.31–0.96; I^2=56%).

Conclusions: Overall effectiveness of OAD adherence-enhancing interventions that have been tested is small. Helping patients cope with side effects or formulate desired treatment outcomes could impact the effectiveness of OAD adherence-enhancing interventions. However, only interventions that include helping patients to cope with side effects appear to be particularly effective in improving OAD adherence.

INTRODUCTION

In 2011, approximately 366 million people worldwide suffered from diabetes, and this number could reach 552 million by 2030 (1, 2). In 2011, the global diabetes burden was estimated to be at least US$465 billion, and this represented 11% of adult healthcare costs worldwide (2). A large proportion of this burden is attributed to type 2 diabetes which accounts for more than 90% of all diabetes cases (3).

To prevent microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular and cerebrovascular diseases and leg amputations) diabetes complications, patients with type 2 diabetes should achieve certain target blood glucose levels (typically, glycated hemoglobin less than 7%) through regular physical activity, a healthy diet with low carbohydrate intake, and appropriate use of drug treatment (4). Oral antidiabetic drugs (OADs), when taken as recommended, can substantially contribute to achieving metabolic control (5, 6), which thereby improves quality of life (5). Even though insulin can be used alone or in combination with OADs, nearly 60% of individuals with type 2 diabetes use only OADs to control their diabetes (7). Unfortunately, patient adherence to OAD treatment is often poor (8, 9), which contributes to suboptimal metabolic control (10, 11), increased diabetes complications and hospitalizations (12, 13), and increased health care expenditures (14).

Adherence to OAD treatment could be optimized by exposing patients to effective behavior change interventions. Two systematic reviews (15, 16) have been previously conducted, but these focused on only OAD adherence-enhancing interventions delivered by pharmacists and did not assess the overall effectiveness of the interventions. In addition, recent advances in the coding of published behavior change interventions have made it possible to conduct more rigorous, standardized analyses of intervention components (17). Moreover, there is growing evidence that not only intervention groups but also control groups in adherence-enhancing interventions are exposed to effective behavioral support (e.g., as part of usual care) that can vary between studies and impact intervention effects. Hence, we performed a systematic review and a meta-analysis of the effectiveness of interventions aimed at enhancing OAD adherence in adults with type 2 diabetes. The aim was to identify the behavior change techniques (BCTs) delivered to both the intervention and the control groups, estimate the pooled intervention effect size, and explore which of the BCTs that were applied in the intervention groups (but not the control groups) modified this pooled effect size.

RESEARCH DESIGN AND METHODS

The present study was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18, 19).

Literature search

We conducted a literature search of studies using Medline (via PubMed), Embase, Psych-Info, the Cochrane Library, CINAHL PLUS with Full Text, Current Contents Connect (Social & Behavioral Sciences (SBS) (from 1998 to present), Clinical Medicine (CM) (from 1998 to present), Engineering, Computing & Technology (ECT) (from 1998 to present), and Web of Science. We searched databases from their start dates through September 3, 2013 (see search strategies in Supplementary-Table S_1 and the results in Figure 1). Search results were downloaded and imported directly into EndNote, version X4 (20). No language restriction was applied. An information scientist (FB) assisted us in developing an optimal search strategy.

Eligibility criteria and Study selection

We defined eligibility criteria based on PICOS (participants, intervention, comparator, outcomes, study design) (18). Types of participants: All studies that focused on adults aged 18 years or over with type 2 diabetes who used OADs. Types of interventions: Interventions with at least one component aimed at improving OAD adherence, regardless of the methods or techniques used. Comparator: Individuals with type 2 diabetes who were exposed to usual care and/or to an intervention of any sort. Outcomes: The main outcome was OAD adherence. We included original studies in which OAD adherence was measured both before and after the intervention. Study designs: We included randomized controlled trials, quasi-experimental studies and controlled pre-/posttest studies.

Duplicates were removed, after which two coders (authors HTVZ and NP) screened the titles, abstracts and full texts of the remaining articles. The coders also manually searched the bibliographic reference lists of eligible articles and previous systematic reviews. If the results of a study were reported in more than one publication, we retained only the publication with the most complete results. We included publications on the same study only if they focused on different populations.

Data extraction

A data collection form based on the data collection guide of the Cochrane Collaboration was developed (see details in Supplementary-Table S2). Two coders independently extracted data from the selected studies. Disagreements were resolved by consensus after discussion or, if necessary, by a third author. To obtain missing information on the primary outcome or to clarify information, corresponding authors were contacted by email. All corresponding authors of the selected studies were also asked to send us their intervention protocols, manuals or any documents that described the interventions offered to the control and intervention groups. Descriptions of usual care/standard care

components were not requested for multi-site studies because this information was assumed to be unavailable to the study authors. If there was no reply after two weeks, a reminder email was sent.

Study details - authors HTVZ and NP extracted the following information: general information such as first author's names and year of publication; population and setting; methods; participants; intervention groups; outcomes; results; and the main conclusions of the study authors.

Categorization of intervention components - HTVZ prepared the available documents and corresponding articles for coding by concealing the names of the study authors, the journals of publication, the results, the discussions and the conclusions. To identify the BCTs used in the selected studies, two coders (authors LAV and LaG) independently categorized the components of the interventions in both the intervention and control groups using the coding manual for BCTs in adherence interventions (see Supplementary-Table S_3), adapted to diabetes care with the support of the original author (author MdB) (21, 22). Disagreements in codification were resolved by consensus between the two coders.

Assessment of internal (risk of bias) and external validities - HTVZ and NP independently assessed the internal (risk of bias) and external validity of the selected studies using a checklist based on the Methods for the development of NICE public health guidance (23). The checklist has five sections (see Supplementary-Table S_2, item 10), namely, population, allocation, outcomes, analyses, and external and internal validity summary. The items are rated as good, medium, low, not reported, or not applicable. The coders also rated overall study quality by grading internal and external validities as good, medium, or low.

Data synthesis and analysis

All selected studies were described in detail with regard to each study and each OAD adherence measure as well as intervention and control group characteristics.

Because there were between-study differences in the instruments used to measure OAD adherence, we estimated the individual intervention effect sizes on OAD adherence using Hedges's g (bias-corrected standardized mean difference [SMD]) and a 95% confidence interval (CI) (24). When there was more than one type of OAD adherence measure, only the one for which there were both pre- and post-intervention values or the one used in most of the studies was included. When there was more than one post-intervention measure, we considered the one that was nearest the end of the intervention.

When adherence was reported on a continuous scale, we directly computed Hedges's g based on sample sizes and adherence means of both intervention and control groups. In order to be able to pool studies in which OAD adherence was reported as a binary variable with those in which it was reported as a continuous variable, we made the following transformation for OAD adherence binary variables. We calculated the odds ratio (OR), converted it to Cohen's d using the formula $d = 3^{1/2} \ln(OR)/ \pi$ (24, 25), which was then transformed into SMD (Hedges's g) = [(1– $3/(4N_1 + 4N_2 – 9))*d]$ with N_1= intervention group sample size and N_2= control group sample size.(24) Our review focused on a wide variety of behavioral interventions aiming to enhance oral antidiabetic drug adherence. Therefore, we anticipated there would be heterogeneity in the estimate of the pooled intervention effect size. In order to take into account this potential heterogeneity, random-effects model was used to estimate the pooled intervention effect size and its 95% interval confidence (CI) (26). Pooled SMD values of < 0.2, ≥ 0.2 to <0.5, ≥ 0.5 to < 0.8, or ≥ 0.8 were considered very small, small, medium and large, respectively (27).

Potential heterogeneity was tested by Chi-squared test and quantified with the Higgins I^2 statistic (28, 29). We used a forest plot to analyze the pooled intervention effect size on OAD adherence. We also performed multiple sensitivity analyses, namely, analyzing the influence of individual studies on heterogeneity by removing each study one by one in the estimation of the pooled SMD. Only studies with at least medium internal validity were included in the meta-analysis (18).

We analyzed the influence of BCTs on the pooled intervention effect size by comparing the pooled intervention SMD containing a given BCT with the pooled SMD of those in which that BCT was not applied. For these analyses, we considered only the BCTs that were applied in intervention groups (i.e., not in control groups) in a given trial. Because, multiple comparison tests were done, we used the Bonferroni method to correct the observed p-value from the significance tests by multiplying this p-value by the number of tests (30).

Subgroup analyses were conducted when possible, i.e. for subgroups of at least three studies. We assessed the potential publication bias with funnel plot and nonparametric "trim and fill" methods (31) using Macro PubBias SAS (32). Analyses were conducted using RevMan (version 5.2) (33) and SAS (version 9.3) (34) software.

RESULTS

Study selection and study characteristics

Out of 7,561 studies reviewed, a total of 14 were selected to be included in the qualitative analysis. Agreement between reviewers was substantial (35) for title and abstract screening (kappa= 0.65) and for full-text selection (kappa= 0.72). The study selection process is described in Figure 1.

Participants' sociodemographic characteristics at baseline and at follow-up are summarized in Table 1. The studies were published between 2004 and 2013 with five studies published in 2012 (36-40). The majority of studies were conducted in the United States (36, 38, 39, 41-46). All studies but one (42) were randomized controlled trials, and were conducted in diverse settings. Sample sizes ranged from 33 to 526 participants, except for the study by Brennan et al., in which 29,247 individuals were included (42). Participants' mean ages varied from 51.5 to 63.2 years. At baseline, hemoglobin A1c (HbA1c) mean rates varied from 7.2% to 9.2%, and participants' average OAD adherence levels were suboptimal in six studies (36, 40, 41, 43, 44, 47). Study follow-up periods ranged from three to 24 months (median= 6.5 months), and study retention rates ranged from 82.6% to 100%.

Assessment of internal (risk of bias) and external validities

The internal and external validities of the included studies are presented in Supplementary Table S_4. Internal validity was good in four studies (43, 45-47), medium in seven studies (36-41, 44) and low in three studies (42, 48, 49). Hence, 11 studies had at medium-high internal validity and were eligible for meta-analysis. External validity was medium in four studies (36, 37, 39, 46) and low in the other 10 (38, 40-45, 47-49).

OAD adherence measure characteristics

The characteristics of OAD adherence measures are described in Supplementary Table S_5. OAD adherence was the primary outcome in eight studies (36-41, 44, 47). It was self-reported in seven studies (37, 40, 43-47) and was measured with medication event monitoring systems (MEMS) in five studies (36, 37, 41, 44, 45) and with prescription claims data in three (38, 39, 46). Two instruments (MEMS or prescription claims data plus self-report) were used in three studies (37, 44, 46).

Intervention characteristics

The intervention characteristics are summarized in Table 2. Only one intervention (37) was guided by theory, and this intervention used the theory of planned behavior (50). The intervention implementation periods ranged from one day to 24 months. The planned numbers of sessions with patients ranged from one to 72. Intervention delivery mode was dual in seven studies (36, 38, 39, 41, 43, 44, 46), with phone calls being the most-used mode (36, 38, 39, 41, 43, 46) in addition to face-to-face meetings (36, 38, 39, 41), group meetings (43), and mail (46). An intervention guide

or a manual was used by those who conducted the intervention in seven studies (36, 37, 39, 41, 43, 45, 46). The authors report having assessed intervention fidelity, i.e., how the interventionists complied with the intervention guide or manual, in only two studies (39, 45). The interventionists were trained and coached during intervention implementation in seven studies (36, 37, 39, 41, 43, 45, 46). Interventions were conducted by the researchers in four studies (36, 40, 41, 44) and by nurses in three (37, 38, 47). In the remaining four studies, nurses and patients (peer support) (43), community health workers (45), pharmacists (39), or health educators (46) conducted the interventions.

Components of the interventions in the control and intervention groups

Table 2 presents the components of the interventions offered to the control and intervention groups. Interventions offered to control groups, especially usual care, could not be categorized in five out of the 11 studies (36-39, 41), but all interventions (11 studies) in the intervention groups were categorized. In total, 25 different BCTs were categorized in the intervention and control groups, and 22 of these were applied in only the intervention groups for a given trial. Eight out of these 22 BCTs were offered in three studies or more: "provide general information" (36-39, 41); "plan coping responses" (38, 39, 46, 47); "self-report of behavior" (36, 38, 41); "reinforce motivational progress" (37, 38, 41); "specific goal setting" (37-39, 46); "continuous professional support" (38, 39, 45); "general intention formation" (37, 38, 45); and "cope with side effects" (36, 39, 41). Not taking into account "usual care," the total numbers of BCTs offered in intervention groups ranged from two to 11 (median= 7) and it varied from zero to six (median= 2) in control groups.

Pooled intervention effect size on OAD adherence

Intervention effects on OAD adherence were both positive and statistically significant ($P< 0.05$) in six studies (36, 39, 41, 44, 46, 47), null in four studies (37, 38, 43, 45), and negative in one study (40). A total of 10 studies were included in the meta-analysis because the intervention effect size could not be calculated for one study (44). Adherence was either measured on a dichotomous (36, 41, 43, 45, 46) or continuous scale (37, 38, 39, 40, 47). When the reported adherence measure was dichotomous, we used the categorization cut-off value as reported in the study articles. In each of the 10 study articles there was only one intervention for which it was possible to estimate the effect size on OAD adherence. We pooled the effect sizes of these 10 behavioral interventions in our meta-analysis. Since the heterogeneity was high ($I^2= 82\%$; (p-value< 0.001), we only reported the results of random-effects model (see Figure 2). The pooled intervention effect size was small (0.21, 95% CI= -0.05 – 0.47, p-value= 0.120).

Influence of BCTs on pooled intervention effect size

We examined whether the eight unique BCTs offered in at least three studies explained the heterogeneity in intervention effect sizes (see Table 3). In total, eight comparison tests were done for the analyses of the influence of BCTs on pooled intervention effect size. We observed a statistically significant difference in pooled effect size between interventions that did and did not apply "cope with side effects" and that did and did not apply "general intention formation." Interventions in which "cope with side effects" was applied had a pooled SMD of 0.64 (95% CI= 0.31 – 0.96) versus 0.02 (95% CI= -0.25 – 0.28) for those that did not (the subgroup difference's p-value= 0.003, p-value corrected using the Bonferroni method was equal to 0.024). Interventions that applied "general intention formation" had a pooled SMD of -0.15 (95% CI= -0.34 – 0.04) and those that did not apply it had a pooled SMD of 0.37 (95% CI= 0.05 – 0.69) (the subgroup difference's p-value= 0.006, p-value corrected using the Bonferroni method was equal to 0.048).

Sensitivity analyses and publication bias

The analysis of heterogeneity showed that excluding any of the 10 included studies did not influence the heterogeneity's value (which ranged from I^2= 79% to I^2= 84%, median= 83%) (see Supplementary-Table S_6). The visual examination of the funnel plot indicated a fairly symmetrical distribution of the studies' pooled effect size. In addition, the nonparametric "trim and fill" method also confirmed the absence of publication bias (see Supplementary-Figure 1).

DISCUSSION

When taken as recommended, OADs can control type 2 diabetes, but many adults who require these drugs do not adhere to their prescribed regimens. Understanding whether adherence-enhancing interventions are effective and which components are involved can inform future interventions and possibly clinical practice. Fourteen trials were included in this systematic review, of which 10 with a medium-high internal validity were included in the meta-analysis. The pooled effect estimate of behavior change interventions on adherence was small with considerable heterogeneity. We explored the influence of eight unique BCTs on the pooled intervention effect size and found that helping patients cope with side effects and formulate desired treatment outcomes (i.e., intention formation) significantly modified the pooled effect size.

The small pooled effect size observed could be explained by a few factors. First, the interventions added only a small number of BCTs to the usual care already provided to the control groups (22). Second, psychosocial theory was used

in only one of the interventions included in our meta-analysis (37), but a literature review suggests that more effective use of behavior change theory may increase intervention effects (51). Third, the level of OAD adherence at baseline was already high in four out of the ten studies (37-39, 45), which decreased the opportunity to improve adherence with an intervention (52). Finally, the small effect observed could be explained by poor intervention delivery (53).

The intervention components offered to intervention and control groups varied in type and number from one study to another. We found that interventions that introduced strategies for patients to cope with side effects had a small pooled effect size. “Cope with side effects" reflected that the intervening physician or pharmacist had actively informed the patients about the side effects and provided solutions for them (e.g., alternative medications) or that the patient could quickly contact his physician or pharmacist between visits in case of side effects (22). This finding is in line with the literature that suggests that side effects are common and also one of the most important barriers to adherence to OAD treatment (54, 55). Hence, although it would appear to be obvious, one recommendation for clinical practice would be to more routinely and systematically assess side effects and help patients overcome them. Our results suggest that the use of "general intention formation" in interventions might slightly decrease OAD adherence. However, this result must be interpreted with caution in light of the exploratory nature of these analyses. Our explanation for this counterintuitive finding is that in studies in which “general intention formation” was part of the intervention, study participants had higher OAD adherence at baseline. Moreover, the BCT “cope with side effects” was only applied in the studies that did not apply the BCT “general intention formation”, those latter studies being the comparison group for the BCT “general intention formation.” Therefore, our observation of a decrease in adherence when the BCT “general intention formation” is applied might be due to the fact that this BCT was indirectly compared to BCT “cope with side effects” this latter being effective at enhancing OAD adherence.

Strengths and limitations

This study is one of the few in the field of medication adherence to code the components of interventions and attempt to obtain appropriate descriptions of the support provided to control groups as part of usual care. Two independent coders conducted all of the coding, and we selected only quality studies for the meta-analyses. Moreover, all studies included in our meta-analysis were RCTs. Therefore, one could expect some patient’s characteristics that are likely to be associated with medication adherence (e.g. depression) would be equally distributed in the intervention and control groups. The MPR was used to measure adherence in two studies (39, 46). Since the MPR can in theory be

greater than 100%, including studies using the MPR could have inflated to some extent the effect size in a clinically non-relevant way. Although the authors of one study (46) did not mention how they handled cases of MPR greater than 100%, in the other study (39) the MPR was capped at 100%. Moreover, in our sensitivity analyses, excluding the effect size from those two studies had no impact on the pooled intervention effect size estimate. Our review also has some limitations. First, we classified SMDs as small, medium or large as suggested by Cohen. However, when interpreting these SMDs, one should be aware that the clinical significance of such effect size for patient health is unclear. Second, the small number of studies included limited the possibility of exploring the influence of individual BCTs on intervention effectiveness. This is a common issue in meta-analysis (56-58). Third, despite our considerable efforts to obtain comprehensive descriptions of the adherence support provided to the intervention and control groups from the study authors (because the articles tended to lack the appropriate level of detail), these could not always be obtained. Hence, more BCTs might have been applied in both arms than we were able to determine. This is a common problem that illustrates the importance of improved intervention and control group descriptions in behavior change intervention trials (59, 60). In addition, in the analyses that explored the influence of individual BCTs, the pooled effect sizes obtained from the subgroup analyses may have been confounded by the unmeasured effects of other intervention characteristics (61). Finally, the majority of the studies were conducted in the United States, which limits the generalizability of the findings.

Implications for clinicians and policymakers

Our paper provides evidence-based information on the important components of adherence-enhancing interventions in adults with type 2 diabetes. This knowledge is crucial for a wide variety of health care professionals (physicians, pharmacists, nurses, and health educators), patients, researchers and policy makers who are interested in enhancing OAD adherence. Researchers could use the findings of this review to develop more efficient interventions to enhance OAD adherence. About health care professionals, the findings of this review could help them to identify effective adherence-enhancing interventions that could be implemented in their practice. This paper could also inform policymakers' decisions regarding the financing, the design, the implementation, and the evaluation of adherence-enhancing intervention programs. The findings of this review might ultimately increase the quality of care by allowing patients to receive a better support in the management of their disease.

CONCLUSIONS

Behavior change interventions seem to have a small, favorable effect on adherence to OAD treatment. Interventions that include helping people cope with their side effects seem to be particularly effective in improving adherence to OAD treatment, and we recommend including this in OAD adherence-enhancing interventions. Future studies with better-designed and better-reported interventions are required to identify other behavior change techniques that could benefit patients. Researchers should also make efforts to better capture the content of usual care at the moment behavioral change interventions are offered.

REFERENCES

1. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94: 311-21.

2. Kozak BM, Tjota MY, Close KL. Journal of Diabetes News. International Diabetes Federation (IDF) highlights growing global impact of diabetes in 5th edition of the Diabetes Atlas. Journal of Diabetes. 2012; 4: 8-17.

3. OMS. Organisation mondiale de la santé . Aide-mémoire N°312: Diabète. 2012.

4. Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Bruxelles, Belgium: International Diabetes Federation, 2012.

5. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. JAMA. 1998; 280: 1490-6.

6. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010; 33: 1859-64.

7. Dodd AH, Colby MS, Boye KS, et al. Treatment approach and HbA(1c) control among US adults with type 2 diabetes: NHANES 1999-2004. Current Medical Research and Opinion. 2009; 25: 1605-13.

8. Lee WC, Balu S, Cobden D, et al. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface. 2006; 19: 31-41.

9. Guenette L, Moisan J, Breton MC, et al. Difficulty adhering to antidiabetic treatment: factors associated with persistence and compliance. Diabetes Metab. 2013; 39: 250-7.

10. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care. 2002; 25: 1015-21.

11. Pladevall M, Williams LK, Potts LA, et al. Clinical outcomes and adherence to medication's measured by claims data in patients with diabetes. Diabetes Care. 2004; 27: 2800-05.

12. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care. 2004; 27: 2149-53.

13. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. Medical care. 2005; 43: 521-30.

14. Salas M, Hughes D, Zuluaga A, et al. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. Value Health. 2009; 12: 915-22.

15. Omran D, Guirguis LM, SH. S. Systematic Review of Pharmacist Interventions to Improve Adherence to Oral Antidiabetic Medications in People with Type 2 Diabetes. Canadian Journal of Diabetes. 2012; 36(5): 292-99.

16. Lindenmeyer A, Hearnshaw H, Vermeire E, et al. Interventions to improve adherence to medication in people with type 2 diabetes mellitus: A review of the literature on the role of pharmacists. Journal of Clinical Pharmacy and Therapeutics. 2006; 31: 409-19.

17. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol. 2008; 27: 379-87.

18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1-34.

19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151: 264-9, W64.

20. Guide d'utilisation – EndNote X4. In: Bibliothèque de l'Université Laval, Québec, Québec, et al., eds.: Université Laval, 2011.

21. de Bruin M, Viechtbauer W, Hospers HJ, et al. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. Health Psychol. 2009; 28: 668-74.

22. de Bruin M, Viechtbauer W, Schaalma HP, et al. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. Arch Intern Med. 2010; 170: 240-50.

23. NICE. Methods for the development of NICE public health guidance (second edition). London: National Institute for Health and Clinical Excellence. , 2009.

24. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to meta-analysis. John Wiley and Sons, Ltd, 2009.

25. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Statistics in Medicine. 2000; 19: 3127-31.

26. Dersimonian R, Laird N. Metaanalysis in Clinical-Trials. Controlled clinical trials. 1986; 7: 177-88.

27. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J.: L. Erlbaum Associates, 1988.

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539-58.

29. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-60.

30. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ. 1995; 310: 170.

31. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56: 455-63.

32. Rendina-Gobioff G, Kromrey JD. PUB_BIAS: A SAS® Macro for Detecting Publication Bias in Meta-Analysis. University of South Florida, Tampa, FL: SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS

Institute Inc. in the USA and other countries. ® indicates USA registration., 2006.

33. The Cochrane Collaboration, Review Manager (RevMan) [Computer program]. Version 5.2. . Copenhagen: The Nordic Cochrane Centre, 2012.

34. SAS Institute Inc. 2011. SAS/QC® 9.3 User's Guide. Cary, NC: SAS Institute Inc., 2011.

35. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics. 1977; 33: 363-74.

36. Bogner HR, Morales KH, Vries HF, et al. Integrated management of type 2 diabetes mellitus and depression treatment to improve medication adherence: a randomized controlled trial. Annals of Family Medicine, 2012.

37. Farmer A, Hardeman W, Hughes D, et al. An explanatory randomised controlled trial of a nurse-led, consultation-based intervention to support patients with adherence to taking glucose lowering medication for type 2 diabetes. BMC Fam Pract. 2012; 13: 30.

38. Lin EH, Korff M, Ciechanowski P, et al. Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. Annals of Family Medicine, 2012.

39. Odegard PS, Christensen DB. MAP study: RCT of a medication adherence program for patients with type 2 diabetes. Journal of the American Pharmacists Association. 2012; 52: 753-+.

40. Zolfaghari M, Mousavifar SA, Pedram S, et al. The impact of nurse short message services and telephone follow-ups on diabetic adherence: which one is more effective? Journal of Clinical Nursing. 2012; 21: 1922-31.

41. Bogner HR, Vries HF. Integrating type 2 diabetes mellitus and depression treatment among African Americans: a randomized controlled pilot trial. The Diabetes educator, 2010.

42. Brennan TA, Dollear TJ, Hu M, et al. An Integrated Pharmacy-Based Program Improved Medication Prescription And Adherence Rates In Diabetes Patients. Health Affairs. 2012; 31: 120-29.

43. Heisler M, Vijan S, Makki F, et al. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. Annals of Internal Medicine, 2010.

44. Rosen MI, Rigsby MO, Salahi JT, et al. Electronic monitoring and counseling to improve medication adherence. Behaviour Research and Therapy, 2004.

45. Rothschild SK, Martin MA, Swider SM, et al. Mexican American Trial of Community Health Workers: A Randomized Controlled Trial of a Community Health Worker Intervention for Mexican Americans With Type 2 Diabetes Mellitus. Am J Public Health. 2013.

46. Walker EA, Shmukler C, Ullman R, et al. Results of a Successful Telephonic Intervention to Improve Diabetes Control in Urban Adults A randomized trial. Diabetes Care. 2011; 34: 2-7.

47. Nesari M, Zakerimoghadam M, Rajab A, et al. Effect of telephone follow-up on adherence to a diabetes therapeutic regimen. Japan journal of nursing science : JJNS, 2010.

48. Mehuys E, Bortel L, Bolle L, et al. Effectiveness of a community pharmacist intervention in diabetes care: a randomized controlled trial. Journal of Clinical Pharmacy and Therapeutics, 2011.

49. Phumipamorn S, Pongwecharak J, Soorapan S, et al. Effects of the pharmacist's input on glycaemic control and cardiovascular risks in Muslim diabetes. Primary Care Diabetes, 2008.

50. Ajzen I. The Theory of Planned Behavior. Organizational behavior and human decision processes 1991; 50, : 179-211.

51. Harvey JN, Lawson VL. The importance of health belief models in determining self-care behaviour in diabetes. Diabet Med. 2009; 26: 5-13.

52. Doggrell SA. Does intervention by an allied health professional discussing adherence to medicines improve this adherence in Type 2 diabetes? Diabet Med. 2010; 27: 1341-9.

53. Bartholomew LK. Planning health promotion programs : an intervention mapping approach. 3rd ed ed. San Francisco: Jossey-Bass, 2011.

54. Chao J, Nau DP, Aikens JE. Patient-reported perceptions of side effects of antihyperglycemic medication and adherence to medication regimens in persons with diabetes mellitus. Clin Ther. 2007; 29: 177-80.

55. Farmer A, Kinmonth AL, Sutton S. Measuring beliefs about taking hypoglycaemic medication among people with Type 2 diabetes. Diabet Med. 2006; 23: 265-70.

56. Denford S, Taylor RS, Campbell JL, et al. Effective Behavior Change Techniques in Asthma Self-Care Interventions: Systematic Review and Meta-Regression. Health Psychol. 2013.

57. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open. 2013; 3.

58. Godin G, Vezina-Im LA, Belanger-Gravel A, et al. Efficacy of interventions promoting blood donation: a systematic review. Transfus Med Rev. 2012; 26: 224-37 e6.

59. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014; 348: g1687.

60. Albrecht L, Archibald M, Arseneau D, et al. Development of a checklist to assess the quality of reporting of knowledge translation interventions using the Workgroup for Intervention Development and Evaluation Research (WIDER) recommendations. Implement Sci. 2013; 8: 52.

61. Gjalt-Jorn Ygram Peters, Marijn de Bruin, Crutzen R. Health Psychology Review (2013): Everything should be as simple as possible, but no simpler: towards a protocol for accumulating evidence regarding the active content of health behaviour change interventions. Health Psychology Review,. 2013: 1-16.

ABSTRACT

Objectives: To estimate the pooled effect size of oral antidiabetic drug (OAD) adherence-enhancing interventions, and to explore which of the behavior change techniques (BCTs) that were applied in the intervention groups modified this pooled intervention effect size.

Methods: We searched relevant studies published until 3 September 2013 on Medline, Embase, PsycInfo, the Cochrane Library, CINAHL, Current Contents Connect, and Web of Science. Selected studies were qualitatively synthesized, and those of at least medium quality were included in the meta-analysis. A random-effects model was used to pool effectiveness (Hedges's g) and to examine heterogeneity (Higgins I^2). We also explored the influence on the pooled effectiveness of unique intervention BCTs (those delivered to the intervention but not control groups in a trial) by estimating their modifying effects.

Results: Fourteen studies were selected for the qualitative synthesis and 10 were included in the meta-analysis. The pooled effectiveness of the interventions was 0.21 (95% CI=-0.05–0.47; I^2=82%). Eight unique BCTs were analyzed. "Cope with side effects" (p-value=0.003) and "general intention formation" (p-value=0.006) had a modifying effect on the pooled effectiveness. The pooled effectiveness of the interventions in which "cope with side effects" was applied was moderate (0.64; 95% CI=0.31–0.96; I^2=56%).

Conclusions: Overall effectiveness of OAD adherence-enhancing interventions that have been tested is small. Helping patients cope with side effects or formulate desired treatment outcomes could impact the effectiveness of OAD adherence-enhancing interventions. However, only interventions that include helping patients to cope with side effects appear to be particularly effective in improving OAD adherence.

INTRODUCTION

In 2011, approximately 366 million people worldwide suffered from diabetes, and this number could reach 552 million by 2030 (1, 2). In 2011, the global diabetes burden was estimated to be at least US$465 billion, and this represented 11% of adult healthcare costs worldwide (2). A large proportion of this burden is attributed to type 2 diabetes which accounts for more than 90% of all diabetes cases (3).

To prevent microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular and cerebrovascular diseases and leg amputations) diabetes complications, patients with type 2 diabetes should achieve certain target blood glucose levels (typically, glycated hemoglobin less than 7%) through regular physical activity, a healthy diet with low carbohydrate intake, and appropriate use of drug treatment (4). Oral antidiabetic drugs (OADs), when taken as recommended, can substantially contribute to achieving metabolic control (5, 6), which thereby improves quality of life (5). Even though insulin can be used alone or in combination with OADs, nearly 60% of individuals with type 2 diabetes use only OADs to control their diabetes (7). Unfortunately, patient adherence to OAD treatment is often poor (8, 9), which contributes to suboptimal metabolic control (10, 11), increased diabetes complications and hospitalizations (12, 13), and increased health care expenditures (14).

Adherence to OAD treatment could be optimized by exposing patients to effective behavior change interventions. Two systematic reviews (15, 16) have been previously conducted, but these focused on only OAD adherence-enhancing interventions delivered by pharmacists and did not assess the overall effectiveness of the interventions. In addition, recent advances in the coding of published behavior change interventions have made it possible to conduct more rigorous, standardized analyses of intervention components (17). Moreover, there is growing evidence that not only intervention groups but also control groups in adherence-enhancing interventions are exposed to effective behavioral support (e.g., as part of usual care) that can vary between studies and impact intervention effects. Hence, we performed a systematic review and a meta-analysis of the effectiveness of interventions aimed at enhancing OAD adherence in adults with type 2 diabetes. The aim was to identify the behavior change techniques (BCTs) delivered to both the intervention and the control groups, estimate the pooled intervention effect size, and explore which of the BCTs that were applied in the intervention groups (but not the control groups) modified this pooled effect size.

RESEARCH DESIGN AND METHODS

The present study was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18, 19).

Literature search

We conducted a literature search of studies using Medline (via PubMed), Embase, Psych-Info, the Cochrane Library, CINAHL PLUS with Full Text, Current Contents Connect (Social & Behavioral Sciences (SBS) (from 1998 to present), Clinical Medicine (CM) (from 1998 to present), Engineering, Computing & Technology (ECT) (from 1998 to present), and Web of Science. We searched databases from their start dates through September 3, 2013 (see search strategies in Supplementary-Table S_1 and the results in Figure 1). Search results were downloaded and imported directly into EndNote, version X4 (20). No language restriction was applied. An information scientist (FB) assisted us in developing an optimal search strategy.

Eligibility criteria and Study selection

We defined eligibility criteria based on PICOS (participants, intervention, comparator, outcomes, study design) (18). Types of participants: All studies that focused on adults aged 18 years or over with type 2 diabetes who used OADs. Types of interventions: Interventions with at least one component aimed at improving OAD adherence, regardless of the methods or techniques used. Comparator: Individuals with type 2 diabetes who were exposed to usual care and/or to an intervention of any sort. Outcomes: The main outcome was OAD adherence. We included original studies in which OAD adherence was measured both before and after the intervention. Study designs: We included randomized controlled trials, quasi-experimental studies and controlled pre-/posttest studies.

Duplicates were removed, after which two coders (authors HTVZ and NP) screened the titles, abstracts and full texts of the remaining articles. The coders also manually searched the bibliographic reference lists of eligible articles and previous systematic reviews. If the results of a study were reported in more than one publication, we retained only the publication with the most complete results. We included publications on the same study only if they focused on different populations.

Data extraction

A data collection form based on the data collection guide of the Cochrane Collaboration was developed (see details in Supplementary-Table S2). Two coders independently extracted data from the selected studies. Disagreements were resolved by consensus after discussion or, if necessary, by a third author. To obtain missing information on the primary outcome or to clarify information, corresponding authors were contacted by email. All corresponding authors of the selected studies were also asked to send us their intervention protocols, manuals or any documents that described the interventions offered to the control and intervention groups. Descriptions of usual care/standard care

components were not requested for multi-site studies because this information was assumed to be unavailable to the study authors. If there was no reply after two weeks, a reminder email was sent.

Study details - authors HTVZ and NP extracted the following information: general information such as first author's names and year of publication; population and setting; methods; participants; intervention groups; outcomes; results; and the main conclusions of the study authors.

Categorization of intervention components - HTVZ prepared the available documents and corresponding articles for coding by concealing the names of the study authors, the journals of publication, the results, the discussions and the conclusions. To identify the BCTs used in the selected studies, two coders (authors LAV and LaG) independently categorized the components of the interventions in both the intervention and control groups using the coding manual for BCTs in adherence interventions (see Supplementary-Table S_3), adapted to diabetes care with the support of the original author (author MdB) (21, 22). Disagreements in codification were resolved by consensus between the two coders.

Assessment of internal (risk of bias) and external validities - HTVZ and NP independently assessed the internal (risk of bias) and external validity of the selected studies using a checklist based on the Methods for the development of NICE public health guidance (23). The checklist has five sections (see Supplementary-Table S_2, item 10), namely, population, allocation, outcomes, analyses, and external and internal validity summary. The items are rated as good, medium, low, not reported, or not applicable. The coders also rated overall study quality by grading internal and external validities as good, medium, or low.

Data synthesis and analysis

All selected studies were described in detail with regard to each study and each OAD adherence measure as well as intervention and control group characteristics.

Because there were between-study differences in the instruments used to measure OAD adherence, we estimated the individual intervention effect sizes on OAD adherence using Hedges's g (bias-corrected standardized mean difference [SMD]) and a 95% confidence interval (CI) (24). When there was more than one type of OAD adherence measure, only the one for which there were both pre- and post-intervention values or the one used in most of the studies was included. When there was more than one post-intervention measure, we considered the one that was nearest the end of the intervention.

When adherence was reported on a continuous scale, we directly computed Hedges's g based on sample sizes and adherence means of both intervention and control groups. In order to be able to pool studies in which OAD adherence was reported as a binary variable with those in which it was reported as a continuous variable, we made the following transformation for OAD adherence binary variables. We calculated the odds ratio (OR), converted it to Cohen's d using the formula $d = 3^{1/2} \ln(OR)/\pi$ (24, 25), which was then transformed into ~~and estimated~~ SMD (Hedges's g) = $[(1–3/(4N_1 + 4N_2 – 9))*d]$ with N_1= intervention group sample size and N_2= control group sample size.(24) Our review focused on a wide variety of behavioral interventions aiming to enhance oral antidiabetic drug adherence. Therefore, we anticipated there would be heterogeneity in the estimate of the pooled intervention effect size. In order to take into account this potential heterogeneity, random-effects model was used to estimate the pooled intervention effect size and its 95% interval confidence (CI) ~~To calculate the pooled effect size on OAD adherence and its 95% CI, we planned to first conduct a fixed-effects meta-analysis and to turn it into a random-effects model if heterogeneity was high~~ (26). Pooled SMD values of < 0.2, ≥ 0.2 to <0.5, ≥ 0.5 to < 0.8, or ≥ 0.8 were considered very small, small, medium and large, respectively (27).

Potential heterogeneity was tested by Chi-squared test and quantified with the Higgins I^2 statistic (28, 29). We used a forest plot to analyze the pooled intervention effect size on OAD adherence. We also performed multiple sensitivity analyses, namely, analyzing the influence of individual studies on heterogeneity by removing each study one by one in the estimation of the pooled SMD. Only studies with at least medium internal validity were included in the meta-analysis (18).

We analyzed the influence of BCTs on the pooled intervention effect size by comparing the pooled intervention SMD containing a given BCT with the pooled SMD of those in which that BCT was not applied. For these analyses, we considered only the BCTs that were applied in intervention groups (i.e., not in control groups) in a given trial. Because, multiple comparison tests were done, we used the Bonferroni method to correct the observed p-value from the significance tests by multiplying this p-value by the number of tests (30).

Subgroup analyses were conducted when possible, i.e. for subgroups of at least three studies. We assessed the potential publication bias with funnel plot and nonparametric "trim and fill" methods (31) using Macro PubBias SAS (32). Analyses were conducted using RevMan (version 5.2) (33) and SAS (version 9.3) (34) software.

RESULTS

Study selection and study characteristics

Out of 7,561 studies reviewed, a total of 14 were selected to be included in the qualitative analysis. Agreement between reviewers was substantial (35) for title and abstract screening (kappa= 0.65) and for full-text selection (kappa= 0.72). The study selection process is described in Figure 1.

Participants' sociodemographic characteristics at baseline and at follow-up are summarized in Table 1. The studies were published between 2004 and 2013 with five studies published in 2012 (36-40). The majority of studies were conducted in the United States (36, 38, 39, 41-46). All studies but one (42) were randomized controlled trials, and were conducted in diverse settings. Sample sizes ranged from 33 to 526 participants, except for the study by Brennan et al., in which 29,247 individuals were included (42). Participants' mean ages varied from 51.5 to 63.2 years. At baseline, hemoglobin A1c (HbA1c) mean rates varied from 7.2% to 9.2%, and participants' average OAD adherence levels were suboptimal in six studies (36, 40, 41, 43, 44, 47). Study follow-up periods ranged from three to 24 months (median= 6.5 months), and study retention rates ranged from 82.6% to 100%.

Assessment of internal (risk of bias) and external validities

The internal and external validities of the included studies are presented in Supplementary Table S_4. Internal validity was good in four studies (43, 45-47), medium in seven studies (36-41, 44) and low in three studies (42, 48, 49). Hence, 11 studies had at medium-high internal validity and were eligible for meta-analysis. External validity was medium in four studies (36, 37, 39, 46) and low in the other 10 (38, 40-45, 47-49).

OAD adherence measure characteristics

The characteristics of OAD adherence measures are described in Supplementary Table S_5. OAD adherence was the primary outcome in eight studies (36-41, 44, 47). It was self-reported in seven studies (37, 40, 43-47) and was measured with medication event monitoring systems (MEMS) in five studies (36, 37, 41, 44, 45) and with prescription claims data in three (38, 39, 46). Two instruments (MEMS or prescription claims data plus self-report) were used in three studies (37, 44, 46).

Intervention characteristics

The intervention characteristics are summarized in Table 2. Only one intervention (37) was guided by theory, and this intervention used the theory of planned behavior (50). The intervention implementation periods ranged from one day to 24 months. The planned numbers of sessions with patients ranged from one to 72. Intervention delivery mode was dual in seven studies (36, 38, 39, 41, 43, 44, 46), with phone calls being the most-used mode (36, 38, 39, 41, 43, 46) in addition to face-to-face meetings (36, 38, 39, 41), group meetings (43), and mail (46). An intervention guide

or a manual was used by those who conducted the intervention in seven studies (36, 37, 39, 41, 43, 45, 46). The authors report having assessed intervention fidelity, i.e., how the interventionists complied with the intervention guide or manual, in only two studies (39, 45). The interventionists were trained and coached during intervention implementation in seven studies (36, 37, 39, 41, 43, 45, 46). Interventions were conducted by the researchers in four studies (36, 40, 41, 44) and by nurses in three (37, 38, 47). In the remaining four studies, nurses and patients (peer support) (43), community health workers (45), pharmacists (39), or health educators (46) conducted the interventions.

Components of the interventions in the control and intervention groups

Table 2 presents the components of the interventions offered to the control and intervention groups. Interventions offered to control groups, especially usual care, could not be categorized in five out of the 11 studies (36-39, 41), but all interventions (11 studies) in the intervention groups were categorized. In total, 25 different BCTs were categorized in the intervention and control groups, and 22 of these were applied in only the intervention groups for a given trial. Eight out of these 22 BCTs were offered in three studies or more: "provide general information" (36-39, 41); "plan coping responses" (38, 39, 46, 47); "self-report of behavior" (36, 38, 41); "reinforce motivational progress" (37, 38, 41); "specific goal setting" (37-39, 46); "continuous professional support" (38, 39, 45); "general intention formation" (37, 38, 45); and "cope with side effects" (36, 39, 41). Not taking into account "usual care," the total numbers of BCTs offered in intervention groups ranged from two to 11 (median= 7) and it varied from zero to six (median= 2) in control groups.

Pooled intervention effect size on OAD adherence

Intervention effects on OAD adherence were both positive and statistically significant (P< 0.05) in six studies (36, 39, 41, 44, 46, 47), null in four studies (37, 38, 43, 45), and negative in one study (40). A total of 10 studies were included in the meta-analysis because the intervention effect size could not be calculated for one study (44). Adherence was either measured on a dichotomous (36, 41, 43, 45, 46) or continuous scale (37, 38, 39, 40, 47). When the reported adherence measure was dichotomous, we used the categorization cut-off value as reported in the study articles. In each of the 10 study articles there was only one intervention for which it was possible to estimate the effect size on OAD adherence. We pooled the effect sizes of these 10 behavioral interventions in our meta-analysis. Since the heterogeneity was high (I^2= 82%; (*p*-value< 0.001), we only reported the results of random-effects model (see Figure 2). The pooled intervention effect size was small (0.21, 95% CI= -0.05 – 0.47, *p*-value= 0.120).

Influence of BCTs on pooled intervention effect size

We examined whether the eight unique BCTs offered in at least three studies explained the heterogeneity in intervention effect sizes (see Table 3). In total, eight comparison tests were done for the analyses of the influence of BCTs on pooled intervention effect size. We observed a statistically significant difference in pooled effect size between interventions that did and did not apply "cope with side effects" and that did and did not apply "general intention formation." Interventions in which "cope with side effects" was applied had a pooled SMD of 0.64 (95% CI= 0.31 – 0.96) versus 0.02 (95% CI= -0.25 – 0.28) for those that did not (the subgroup difference's p-value= 0.003, p-value corrected using the Bonferroni method was equal to 0.024). Interventions that applied "general intention formation" had a pooled SMD of -0.15 (95% CI= -0.34 – 0.04) and those that did not apply it had a pooled SMD of 0.37 (95% CI= 0.05 – 0.69) (the subgroup difference's p-value= 0.006, p-value corrected using the Bonferroni method was equal to 0.048).

Sensitivity analyses and publication bias

The analysis of heterogeneity showed that excluding any of the 10 included studies did not influence the heterogeneity's value (which ranged from I^2= 79% to I^2= 84%, median= 83%) (see Supplementary-Table S_6). The visual examination of the funnel plot indicated a fairly symmetrical distribution of the studies' pooled effect size. In addition, the nonparametric "trim and fill" method also confirmed the absence of publication bias (see Supplementary-Figure 1).

DISCUSSION

When taken as recommended, OADs can control type 2 diabetes, but many adults who require these drugs do not adhere to their prescribed regimens. Understanding whether adherence-enhancing interventions are effective and which components are involved can inform future interventions and possibly clinical practice. Fourteen trials were included in this systematic review, of which 10 with a medium-high internal validity were included in the meta-analysis. The pooled effect estimate of behavior change interventions on adherence was small with considerable heterogeneity. We explored the influence of eight unique BCTs on the pooled intervention effect size and found that helping patients cope with side effects and formulate desired treatment outcomes (i.e., intention formation) significantly modified the pooled effect size.

The small pooled effect size observed could be explained by a few factors. First, the interventions added only a small number of BCTs to the usual care already provided to the control groups (22). Second, psychosocial theory was used

in only one of the interventions included in our meta-analysis (37), but a literature review suggests that more effective use of behavior change theory may increase intervention effects (51). Third, the level of OAD adherence at baseline was already high in four out of the ten studies (37-39, 45), which decreased the opportunity to improve adherence with an intervention (52). Finally, the small effect observed could be explained by poor intervention delivery (53).

The intervention components offered to intervention and control groups varied in type and number from one study to another. We found that interventions that introduced strategies for patients to cope with side effects had a small pooled effect size. “Cope with side effects" reflected that the intervening physician or pharmacist had actively informed the patients about the side effects and provided solutions for them (e.g., alternative medications) or that the patient could quickly contact his physician or pharmacist between visits in case of side effects (22). This finding is in line with the literature that suggests that side effects are common and also one of the most important barriers to adherence to OAD treatment (54, 55). Hence, although it would appear to be obvious, one recommendation for clinical practice would be to more routinely and systematically assess side effects and help patients overcome them.

Our results suggest that the use of "general intention formation" in interventions might slightly decrease OAD adherence. However, this result must be interpreted with caution in light of the exploratory nature of these analyses. Our explanation for this counterintuitive finding is that in studies in which “general intention formation” was part of the intervention, study participants had higher OAD adherence at baseline. Moreover, the ~~potentially effective~~ BCT “cope with side effects” was only applied in the studies that did not apply the BCT “general intention formation~~.~~”, those latter studies being the comparison group for the BCT “general intention formation.” Therefore, our observation of a decrease in adherence when the BCT “general intention formation” is applied might be due to the fact that this BCT was indirectly compared to BCT “cope with side effects” this latter being effective at enhancing OAD adherence. ~~These associations suggest that confounding may be a potential explanation for this negative association.~~

Strengths and limitations

This study is one of the few in the field of medication adherence to code the components of interventions and attempt to obtain appropriate descriptions of the support provided to control groups as part of usual care. Two independent coders conducted all of the coding, and we selected only quality studies for the meta-analyses. Moreover, all studies included in our meta-analysis were RCTs. Therefore, one could expect some patient’s characteristics that are likely

to be associated with medication adherence (e.g. depression) would be equally distributed in the intervention and control groups. The MPR was used to measure adherence in two studies (39, 46). Since the MPR can in theory be greater than 100%, including studies using the MPR could have inflated to some extent the effect size in a clinically non-relevant way. Although the authors of one study (46) did not mention how they handled cases of MPR greater than 100%, in the other study (39) the MPR was capped at 100%. Moreover, in our sensitivity analyses, excluding the effect size from those two studies had no impact on the pooled intervention effect size estimate. Our review also has some limitations. First, we classified SMDs as small, medium or large as suggested by Cohen. However, when interpreting these SMDs, one should be aware that the clinical significance of such effect size for patient health is unclear. ~~First~~Second, the small number of studies included limited the possibility of exploring the influence of individual BCTs on intervention effectiveness. This is a common issue in meta-analysis (56-58). ~~Second~~Third, despite our considerable efforts to obtain comprehensive descriptions of the adherence support provided to the intervention and control groups from the study authors (because the articles tended to lack the appropriate level of detail), these could not always be obtained. Hence, more BCTs might have been applied in both arms than we were able to determine. This is a common problem that illustrates the importance of improved intervention and control group descriptions in behavior change intervention trials (59, 60). ~~Third~~In addition, in the analyses that explored the influence of individual BCTs, the pooled effect sizes obtained from the subgroup analyses may have been confounded by the unmeasured effects of other intervention characteristics (61). Finally, the majority of the studies were conducted in the United States, which limits the generalizability of the findings.

Implications for clinicians and policymakers

Our paper provides evidence-based information on the important components of adherence-enhancing interventions in adults with type 2 diabetes. This knowledge is crucial for a wide variety of health care professionals (physicians, pharmacists, nurses, and health educators), patients, researchers and policy makers who are interested in enhancing OAD adherence. Researchers could use the findings of this review to develop more efficient interventions to enhance OAD adherence. About health care professionals, the findings of this review could help them to identify effective adherence-enhancing interventions that could be implemented in their practice. This paper could also inform policymakers' decisions regarding the financing, the design, the implementation, and the evaluation of adherence-enhancing intervention programs. The findings of this review might ultimately increase the quality of care by allowing patients to receive a better support in the management of their disease.

CONCLUSIONS

~~Few quality trials that evaluate the impact of adherence interventions and OAD use have been published. Intervention design was rarely based on established behavior change theory, and the adherence support delivered to both intervention and control groups was poorly described. Nevertheless, b~~Behavior change interventions seem to have a small, favorable effect on adherence to OAD treatment. ~~The high heterogeneity in effect sizes was substantially reduced when we distinguished between studies in which interventions focused on addressing patient side effects and those that focused on general intention formation.~~ Interventions that include helping people cope with their side effects seem to be particularly effective in improving adherence to OAD treatment, and we recommend including this in OAD adherence-enhancing interventions. Future studies with better-designed and better-reported interventions are required to identify other behavior change techniques that could benefit patients. Researchers should also make efforts to better capture the content of usual care at the moment behavioral change interventions are offered.

REFERENCES

1. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94: 311-21.

2. Kozak BM, Tjota MY, Close KL. Journal of Diabetes News. International Diabetes Federation (IDF) highlights growing global impact of diabetes in 5th edition of the Diabetes Atlas. Journal of Diabetes. 2012; 4: 8-17.

3. OMS. Organisation mondiale de la santé . Aide-mémoire N°312: Diabète. 2012.

4. Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Bruxelles, Belgium: International Diabetes Federation, 2012.

5. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. JAMA. 1998; 280: 1490-6.

6. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010; 33: 1859-64.

7. Dodd AH, Colby MS, Boye KS, et al. Treatment approach and HbA(1c) control among US adults with type 2 diabetes: NHANES 1999-2004. Current Medical Research and Opinion. 2009; 25: 1605-13.

8. Lee WC, Balu S, Cobden D, et al. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface. 2006; 19: 31-41.

9. Guenette L, Moisan J, Breton MC, et al. Difficulty adhering to antidiabetic treatment: factors associated with persistence and compliance. Diabetes Metab. 2013; 39: 250-7.

10. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care. 2002; 25: 1015-21.

11. Pladevall M, Williams LK, Potts LA, et al. Clinical outcomes and adherence to medication's measured by claims data in patients with diabetes. Diabetes Care. 2004; 27: 2800-05.

12. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care. 2004; 27: 2149-53.

13. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. Medical care. 2005; 43: 521-30.

14. Salas M, Hughes D, Zuluaga A, et al. Costs of medication nonadherence in patients with diabetes mellitus: a systematic review and critical analysis of the literature. Value Health. 2009; 12: 915-22.

15. Omran D, Guirguis LM, SH. S. Systematic Review of Pharmacist Interventions to Improve Adherence to Oral Antidiabetic Medications in People with Type 2 Diabetes. Canadian Journal of Diabetes. 2012; 36(5): 292-99.

16. Lindenmeyer A, Hearnshaw H, Vermeire E, et al. Interventions to improve adherence to medication in people with type 2 diabetes mellitus: A review of the literature on the role of pharmacists. Journal of Clinical Pharmacy and Therapeutics. 2006; 31: 409-19.

17. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol. 2008; 27: 379-87.

18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1-34.

19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151: 264-9, W64.

20. Guide d'utilisation – EndNote X4. In: Bibliothèque de l'Université Laval, Québec, Québec, et al., eds.: Université Laval, 2011.

21. de Bruin M, Viechtbauer W, Hospers HJ, et al. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. Health Psychol. 2009; 28: 668-74.

22. de Bruin M, Viechtbauer W, Schaalma HP, et al. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. Arch Intern Med. 2010; 170: 240-50.

23. NICE. Methods for the development of NICE public health guidance (second edition). London: National Institute for Health and Clinical Excellence. , 2009.

24. Borenstein M, Hedges LV, Higgins JPT, et al. Introduction to meta-analysis. John Wiley and Sons, Ltd, 2009.

25. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Statistics in Medicine. 2000; 19: 3127-31.

26. Dersimonian R, Laird N. Metaanalysis in Clinical-Trials. Controlled clinical trials. 1986; 7: 177-88.

27. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J.: L. Erlbaum Associates, 1988.

28. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539-58.

29. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-60.

30. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ. 1995; 310: 170.

31. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56: 455-63.

32. Rendina-Gobioff G, Kromrey JD. PUB_BIAS: A SAS® Macro for Detecting Publication Bias in Meta-Analysis. University of South Florida, Tampa, FL: SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS

Institute Inc. in the USA and other countries. ® indicates USA registration., 2006.

33. The Cochrane Collaboration, Review Manager (RevMan) [Computer program]. Version 5.2. . Copenhagen: The Nordic Cochrane Centre, 2012.

34. SAS Institute Inc. 2011. SAS/QC® 9.3 User's Guide. Cary, NC: SAS Institute Inc., 2011.

35. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics. 1977; 33: 363-74.

36. Bogner HR, Morales KH, Vries HF, et al. Integrated management of type 2 diabetes mellitus and depression treatment to improve medication adherence: a randomized controlled trial. Annals of Family Medicine, 2012.

37. Farmer A, Hardeman W, Hughes D, et al. An explanatory randomised controlled trial of a nurse-led, consultation-based intervention to support patients with adherence to taking glucose lowering medication for type 2 diabetes. BMC Fam Pract. 2012; 13: 30.

38. Lin EH, Korff M, Ciechanowski P, et al. Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. Annals of Family Medicine, 2012.

39. Odegard PS, Christensen DB. MAP study: RCT of a medication adherence program for patients with type 2 diabetes. Journal of the American Pharmacists Association. 2012; 52: 753-+.

40. Zolfaghari M, Mousavifar SA, Pedram S, et al. The impact of nurse short message services and telephone follow-ups on diabetic adherence: which one is more effective? Journal of Clinical Nursing. 2012; 21: 1922-31.

41. Bogner HR, Vries HF. Integrating type 2 diabetes mellitus and depression treatment among African Americans: a randomized controlled pilot trial. The Diabetes educator, 2010.

42. Brennan TA, Dollear TJ, Hu M, et al. An Integrated Pharmacy-Based Program Improved Medication Prescription And Adherence Rates In Diabetes Patients. Health Affairs. 2012; 31: 120-29.

43. Heisler M, Vijan S, Makki F, et al. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. Annals of Internal Medicine, 2010.

44. Rosen MI, Rigsby MO, Salahi JT, et al. Electronic monitoring and counseling to improve medication adherence. Behaviour Research and Therapy, 2004.

45. Rothschild SK, Martin MA, Swider SM, et al. Mexican American Trial of Community Health Workers: A Randomized Controlled Trial of a Community Health Worker Intervention for Mexican Americans With Type 2 Diabetes Mellitus. Am J Public Health. 2013.

46. Walker EA, Shmukler C, Ullman R, et al. Results of a Successful Telephonic Intervention to Improve Diabetes Control in Urban Adults A randomized trial. Diabetes Care. 2011; 34: 2-7.

47. Nesari M, Zakerimoghadam M, Rajab A, et al. Effect of telephone follow-up on adherence to a diabetes therapeutic regimen. Japan journal of nursing science : JJNS, 2010.

48. Mehuys E, Bortel L, Bolle L, et al. Effectiveness of a community pharmacist intervention in diabetes care: a randomized controlled trial. Journal of Clinical Pharmacy and Therapeutics, 2011.

49. Phumipamorn S, Pongwecharak J, Soorapan S, et al. Effects of the pharmacist's input on glycaemic control and cardiovascular risks in Muslim diabetes. Primary Care Diabetes, 2008.

50. Ajzen I. The Theory of Planned Behavior. Organizational behavior and human decision processes 1991; 50, : 179-211.

51. Harvey JN, Lawson VL. The importance of health belief models in determining self-care behaviour in diabetes. Diabet Med. 2009; 26: 5-13.

52. Doggrell SA. Does intervention by an allied health professional discussing adherence to medicines improve this adherence in Type 2 diabetes? Diabet Med. 2010; 27: 1341-9.

53. Bartholomew LK. Planning health promotion programs : an intervention mapping approach. 3rd ed ed. San Francisco: Jossey-Bass, 2011.

54. Chao J, Nau DP, Aikens JE. Patient-reported perceptions of side effects of antihyperglycemic medication and adherence to medication regimens in persons with diabetes mellitus. Clin Ther. 2007; 29: 177-80.

55. Farmer A, Kinmonth AL, Sutton S. Measuring beliefs about taking hypoglycaemic medication among people with Type 2 diabetes. Diabet Med. 2006; 23: 265-70.

56. Denford S, Taylor RS, Campbell JL, et al. Effective Behavior Change Techniques in Asthma Self-Care Interventions: Systematic Review and Meta-Regression. Health Psychol. 2013.

57. Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. BMJ Open. 2013; 3.

58. Godin G, Vezina-Im LA, Belanger-Gravel A, et al. Efficacy of interventions promoting blood donation: a systematic review. Transfus Med Rev. 2012; 26: 224-37 e6.

59. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014; 348: g1687.

60. Albrecht L, Archibald M, Arseneau D, et al. Development of a checklist to assess the quality of reporting of knowledge translation interventions using the Workgroup for Intervention Development and Evaluation Research (WIDER) recommendations. Implement Sci. 2013; 8: 52.

61. Gjalt-Jorn Ygram Peters, Marijn de Bruin, Crutzen R. Health Psychology Review (2013): Everything should be as simple as possible, but no simpler: towards a protocol for accumulating evidence regarding the active content of health behaviour change interventions. Health Psychology Review,. 2013: 1-16.

Figure

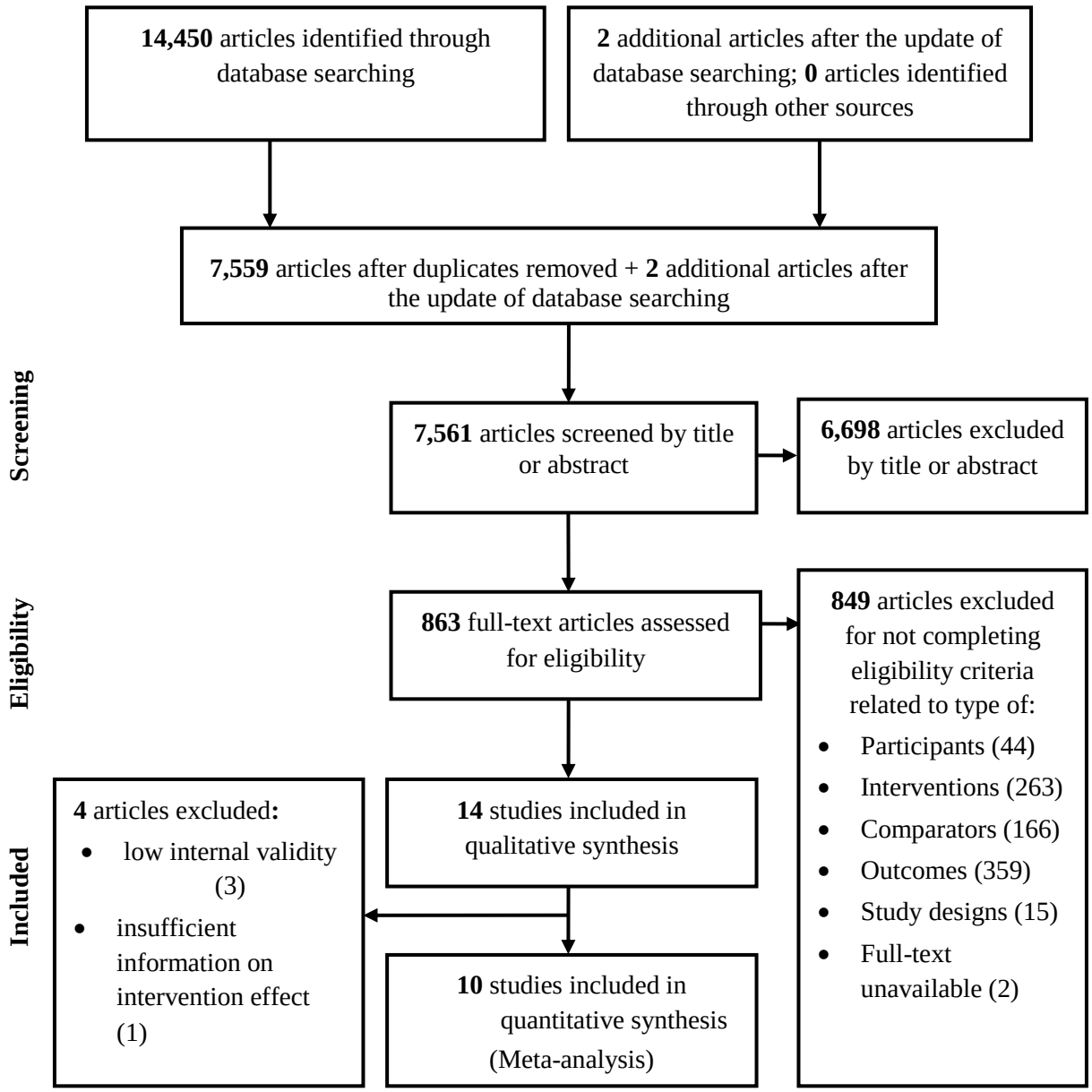


Figure 1: Flow chart of article selection in the systematic review and meta-analysis

Study	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Rothschild, 2013	-0.20	0.203	9.8%	-0.20 (-0.60, 0.20)
Zolfaghari, 2012	-0.36	0.232	9.2%	-0.36 (-0.81, 0.09)
Farmer, 2012	-0.22	0.140	11.1%	-0.22 (-0.49, 0.05)
Bogner, 2012	0.80	0.176	10.4%	0.80 (-0.46, 1.14)
Odegard, 2012	0.40	0.128	11.3%	0.40 (0.15, 0.65)
Lin, 2012	0.00	0.179	10.3%	0.00 (-0.35, 0.35)
Walker, 2011	0.38	0.138	11.2%	0.38 (0.11, 0.65)
Bogner, 2010	0.89	0.315	7.5%	0.89 (0.27, 1.51)
Nesari, 2010	0.80	0.268	8.4%	0.80 (0.27, 1.33)
Heisler, 2010	-0.17	0.155	10.8%	-0.17 (-0.47, 0.13)
Total (95% CI)			**100.0%**	**0.21 (-0.05, 0.47)**

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 51.09$, df = 9 ($P < 0.00001$); $I^2 = 82\%$

Test for overall effect: Z = 1.56 (P = 0.12)

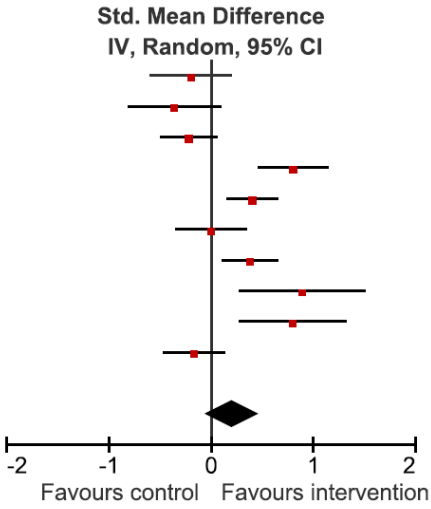


Figure 2: Forest plots of pooled effect size estimates for the 10 studies included in the meta-analysis

Table 1 : Sample, participant characteristics and follow-up

Study 1. Authors 2. Year 3. Design	Sample	Participant characteristics at baseline			Participant follow-up
	1. Sample size 2. Intervention – Control 3. Setting/Country	1. Mean age (SD) 2. Gender (N;% men) 3. Race: white; black; other	4. Low income 5. Diabetes duration	6. HbA1c rate mean (SD) 7. OAD adherence mean	1. Duration 2. Number at the end (I – C) 3. Retention rate (I – C)
1. Rothschild (45) 2. 2013 3. RCT	1. 144 2. 73 – 71 3. Homes +medical center/ U.S.	1. 53.7 years (12.2) 2. 47; 32.6% 3. 0%; 0%; 100%	4. Yes 5. NR	6. 8.3% (2·0) 7. 37% non-adherents	1. 24 months 2. 119 (58 – 61) 3. 82.6% (7.5% – 85.9%)
1. Zolfaghari (40) 2. 2012 3. RCT	1. 80 2. 39 - 41 3. Iranian Diabetes Association/ Iran	1. 52.4 years (NR) 2. 36; 46.8% 3. NR	4. Yes (majority) 5. 8.0 years	6. 9.2% (NR) 7. 75%; 0(low) – 100(high)	1. 6 months 2. 77 (38 – 39) 3. 96.3% (97.4% – 95.1%)
1. Odegard (39) 2. 2012 3. RCT	1. 265 2. 120 – 145 3. Pharmacies/ U.S.	1. 62.8 years (NR) 2. 127; 48.1% 3. NR	4. NR 5. NR	6. Not assessed 7. 85%; 0(low) – 100 (high)	1. 12 months 2. 255 (118 – 137) 3. 96.2% (98.3% – 94.5%)
1. Lin (38) † 2. 2012 3. RCT	1. 214 2. 106 – 108 3. Primary care clinics/ U.S.	1. 56.8 years (11.3) 2. 86; 47.6% 3. NR	4. NR 5. NR	6. 8.0 (NR) 7. 83%; 0(low) – 100(high)	1. 12 months 2. 181 (91 – 90) 3. 84.6% (85.8% – 83.3%)
1. Farmer (37) 2. 2012 3. RCT	1. 211 2. 126 - 85 3. General practices/ UK	1. 63.2 years (10.7) 2. 138; 65.4% 3. NR	4. NR 5. 6.8 years	6. 8.3% (1.2%) 7. 23.6; 5(low) – 25(high)	1. 5 months 2. 195 (114 - 81) 3. 92.4% (90.5% – 95.3%)
1. Brennan (42) * 2. 2012 3. NRCT	1. 29,247 2. 5,123 – 24,124 3. Pharmacies/ U.S.	1. 63.1 years (NR) 2. 16,586; 56.7% 3. NR	4. No 5. NR	6. Not assessed 7. Graph form	1. 18 months 2. NR 3. NR
1. Bogner (36) 2. 2012 3. RCT	1. 182 2. 94 – 88 3. Primary care practices/ U.S.	1. 57.5 years (NR) 2. 58; 32.2% 3. 36.1%; 56.7%; 7.2%	4. NR 5. 11 years	6. 7.2% (NR) 7. 60% non-adherents	1. 3 months 2. 180 (92 – 88) 3. 98.9% (97.8% – 100%)
1. Walker (46) † 2. 2011 3. RCT	1. 526 2. 262 – 264 3. Worker union fund/ U.S.	1. 55.5 years 2. 173; 32.9% 3. 5.9%; 61.6%; 32.5%	4. Yes (majority) 5. 9.2 years	6. 8.6% (median) 7. Measured but NR	1. 12 months 2. 444 (228 – 216) 3. 84.4% (87.0% – 81.8%)

Continued on next page

Table 1 : Sample, participant characteristics and follow-up

Study 1. Authors 2. Year 3. Design	Sample	Participant characteristics at baseline			Participant follow-up
	1. Sample size 2. Intervention – Control 3. Setting/Country	1. Mean age (SD) 2. Gender (N;% men) 3. Race: white; black; other	4. Low income 5. Diabetes duration	6. HbA1c rate mean (SD) 7. OAD adherence mean	1. Duration 2. Number at the end (I – C) 3. Retention rate (I – C)
1. Mehuys (48) * 2. 2011 3. RCT	1. 66 pharmacies (288 patients) 2. 35 (153) – 31 (135) 3. Pharmacies/ Belgium	1. 62.7 years (NR) 2. 151; 52.3% 3. NR	4. NR 5. NR	6. 7.5% (NR) 7. 38.1% (non-adherents, at least 1 time/ year)	1. 6 months 2. 280 (148 – 132) 3. 97.2% (96.7% – 97.8%)
1. Nesari (47) 2. 2010 3. RCT	1. 61 2. 30 – 31 3. Iranian Diabetes Association/ Iran	1. 51.5 years 2. 17; 28.3% 3. NR	4. Yes (majority) 5. ≥2 years (81.7%)	6. 8.9% (NR) 7. 61%; 0(low)–100(high)	1. 12 months 2. 60 (30 – 30) 3. 98.4% (100% – 96.8%)
1. Heisler (43) 2. 2010 3. RCT	1. 244 2. 125 – 119 3. Veterans clinics/U.S.	1. 62.0 years (6.3) 2. 244; 100% 3. 82%; 9%; 9%	4. Yes (majority) 5. NR	6. 8·0% (1·4) 7. 69% non-adherents	1. 6 months 2. 231 (117 – 114) 3. 94.7% (93.6% – 95.8%)
1. Bogner (41) 2. 2010 3. RCT	1. 58 2. 29 – 29 3. Primary care practice/ U.S.	1. 60.0 years (NR) 2. 9; 15.5% 3. 0%; 100%; 0%	4. NR 5. NR	6. 7.3% 7. 66% non-adherents	1. 3 months 2. 58 (29 – 29) 3. 100% (100% – 100%)
1. Phumipamorn (49) * 2. 2008 3. RCT	1. 135 2. 67 – 68 3. Community hospital/ Thailand	1. 54.1% (NR) 2. 21; 16.2% 3. NR	4. NR 5. 6.4 years (NR)	6. 8.7% (1.5) 7. 85%; 0(low)–100(high)	1. 6 months 2. 130 (63 – 67) 3. 96.3% (94.0% – 98.5%)
1. Rosen (44) 2. 2004 3. RCT	1. 33 2. 16 – 17 3. Primary care clinic/ U.S.	1. 62.9 years (NR) 2. NR 3. 72.7%; 27.3%; 0%	4. NR 5. NR	6. 7.5% 7. 60%; 0(low)–100(high)	1. 7 months 2. 33 (16 – 17) 3. 100% (100% – 100%)

*Studies were excluded from the other tables because their methodological quality was low.

†In the study by Walker et al., there were 385 analyzed participants who did not use insulin. In the study by Lin et al., there were 124 analyzed participants who used oral antidiabetic medication, 66 in the intervention group and 58 in the control group.

OAD= oral antidiabetic; SMS= short message service; NR= not reported, RCT= randomized controlled trial; NRCT= non-randomized controlled trial; U.S.= United States; UK= United Kingdom

Table 2: Characteristics and components of interventions in the 10 studies retained of meta-analysis

Study 1. Authors 2. Year 3. RCT	**Intervention characteristics** 1. Psychosocial theory 2. Intervention period 3. Number of sessions	 4. Delivery mode used 5. Guide used 6. Intervention fidelity	**Components of interventions** 1. Intervention group	 2. Control group	**Interventionist** 1. Profile 2. Training 3. Coaching
1. Rothschild(45) 2. 2013 3. RCT	1. Not used 2. 24 months 3. 36	4. Face to face 5. Yes 6. Assessed	EMB; provide general information; plan coping responses; general intention formation†; self-monitoring of behavior; REB; use of social support; practice, guided practice†; feedback: delayed feedback of behavior†; continuous professional support†	EMB provide general information; plan coping responses; use of social support; self-monitoring of behavior; REB	1. CHW 2. Yes 3. Yes
1. Zolfaghari(40) 2. 2012 3. RCT	1. Not used 2. 3 months 3. 72	4. SMS 5. No 6. Not assessed	provide general information; plan coping responses	provide general information; risk communication‡; self-monitoring of behavior‡; self-report of behavior‡; plan coping responses	1. Researcher 2. No 3. No
1. Odegard(39) * 2. 2012 3. RCT	1. Not used 2. 12 months 3. 3.4	4. Face to face + phone calls 5. Yes 6. Assessed	plan coping responses†; provide general information†; specific goal setting†; continuous professional support†; EMB; persuasive argument, belief selection†; cope with side effects†	EMB usual care (cannot be coded)	1. Pharmacists 2. Yes 3. Yes

Continued on next page

Table 2: Characteristics and components of interventions in the 10 studies retained of meta-analysis

Study 1. Authors 2. Year 3. RCT	**Intervention characteristics** 1. Psychosocial theory 2. Intervention period 3. Number of sessions	 4. Delivery mode used 5. Guide used 6. Intervention fidelity	**Components of interventions** 1. Intervention group	 2. Control group	**Interventionist** 1. Profile 2. Training 3. Coaching
1. Lin(38) * 2. 2012 3. RCT	1. Not used 2. 12 months 3. 24 -36	4. Face to face + phone calls 5. No 6. Not assessed	specific goal setting†; reinforcement on motivational progress†; provide general information†; plan coping responses†; formulate goals for maintenance of behavior†; relapse prevention†; continuous professional support†; general intention formation†; reflective listening†; reevaluation of outcomes†; self-report of behavior†; individualize regimen†	Cannot be coded	1. Nurse 2. No 3. No
1. Farmer(37) * 2. 2012 3. RCT	1. Theory of planned behavior 2. 1 day 3. 1	4. In person 5. Yes 6. Not assessed	persuasive argument†; mobilize social norms†; plan coping responses; reinforcement on motivational progress†; provide general information†; specific goal setting†; use of cues†; EMB; self-report of behavior; general intention formation†	EMB; self-report of behavior; usual care (cannot be coded)	1. Nurses 2. Yes 3. Yes
1. Bogner(36) * 2. 2012 3. RCT	1. Not used 2. 3 months 3. 5	4. Face to face + phone calls 5. Yes 6. Not assessed	provide general information†; cope with side-effects†; use of cues†; use of social support†; EMB; self-report of behavior†	EMB; usual care (cannot be coded)	1. Researchers 2. Yes 3. Yes

Continued on next page

Table 2: Characteristics and components of interventions in the 10 studies retained of meta-analysis

Study 1. Authors 2. Year 3. RCT	**Intervention characteristics** 1. Psychosocial theory 2. Intervention period 3. Number of sessions	 4. Delivery mode used 5. Guide used 6. Intervention fidelity	**Components of interventions** 1. Intervention group	 2. Control group	**Interventionist** 1. Profile 2. Training 3. Coaching
1. Walker(46) 2. 2011 3. RCT	1. Not used 2. 12 months 3. 10	4. Phone calls + mail 5. Yes 6. Not assessed	provide general information; plan coping responses†; specific goal setting†; self-report of behavior	provide general information; self-report of behavior	1. Health educators 2. Yes 3. Yes
1. Nesari(47) 2. 2010 3. RCT	1. Not used 2. 3 months 3. 16	4. Phone calls 5. No 6. Not assessed	provide general information; provide opportunities for social comparison; individualized regimen†; plan coping responses†	provide general information; provide opportunities for social comparison	1. Nurses 2. NR 3. NR
1. Heisler(43) 2. 2010 3. RCT	1. Not used 2. 6 months 3. At least once per week	4. Phone calls + in-group 5. Yes 6. Not assessed	provide opportunities for social comparison†; use of social support†; general intention formation; specific goal setting; reevaluation of outcomes; reflective listening; plan coping responses	provide general information‡; reevaluation of outcomes; reflective listening; plan coping responses; specific goal setting; general intention formation	1. Nurses + patients 2. Yes 3. Yes
1. Bogner(41) * 2. 2010 3. RCT	1. Not used 2. 1 month 3. 5	4. Face to face + phone calls 5. Yes 6. Not assessed	provide general information†; reinforcement on motivational progress†; cope with side effects†; self-report of behavior†; EMB	EMB; usual care (cannot be coded)	1. Researchers 2. Yes 3. Yes

* Intervention or usual care in control group could not be coded.
† Behavior change techniques applied in intervention groups but not in the controls
‡ Behavior change techniques applied in control groups but not in the intervention groups
OAD= oral antidiabetic; SMS= short message service; NR= not reported, NA= not applicable; RCT= randomized controlled trial; EMB= electronic monitoring of behavior; REB = reduce environmental barriers; CHW= community health workers

Table 3: Influence of behavior change techniques on pooled intervention effect size

Behavior change techniques	N	Random-effects models			
		Hedges's g	95% CI	*p*-value	I^2
Provide general information					
Applied	5	0.34	-0.06 – 0.74	0.100	86%
Not applied	5	0.08	-0.29 – 0.45	0.680	80%
Test for subgroup differences:				0.350	----
Self-report of behavior					
Applied	3	0.54	-0.06 – 1.14	0.080	84%
Not applied	7	0.08	-0.20 – 0.37	0.660	81%
Test for subgroup differences:				0.170	----
Reinforcement on motivational progress					
Applied	3	0.15	-0.36 – 0.66	0.560	81%
Not applied	7	0.23	-0.08 – 0.55	0.140	83%
Test for subgroup differences:				0.780	----
Plan coping responses					
Applied	5	0.24	-0.07 – 0.55	0.120	79%
Not applied	5	0.17	-0.33 – 0.68	0.500	87%
Test for subgroup differences:				0.820	----
General intention formation*					
Applied	3	-0.15	-0.34 – 0.04	0.120	0%
Not applied	7	0.37	0.05 – 0.69	0.020	82%
Test for subgroup differences:				0.006	----
Specific goal setting					
Applied	4	0.15	-0.16 – 0.46	0.350	79%
Not applied	6	0.27	-0.19 – 0.74	0.250	86%
Test for subgroup differences:				0.660	----
Continuous professional support					
Applied	3	0.09	-0.28 – 0.46	0.630	73%
Not applied	7	0.28	-0.10 – 0.65	0.150	86%
Test for subgroup differences:				0.490	----
Cope with side-effects*					
Applied	3	0.64	0.31 – 0.96	0.000	56%
Not applied	7	0.02	-0.25 – 0.28	0.900	75%
Test for subgroup differences:				0.003	----

N= number of studies; Hedges's g= Std. Mean Difference; I^2= indicator of heterogeneity
*Behavior change technique significantly influencing the pooled intervention effect size

Supplementary-Table S_1: Search strategies according to the database
MEDLINE VIA PUBMED
Population (1)
Diabetes [tiab] OR Diabetes mellitus [tiab] OR type 2 diabetes [tiab] OR "Hypoglycemic Agents/administration and dosage"[Mesh] OR NIDDM [tiab] OR T2DM [tiab] OR T2D [tiab] OR non insulin$ depend$ OR noninsulin$ depend OR MODY [tiab] OR hypoglycemia [tiab] OR glycosylated hemoglobin [tiab] Limits: Title and abstract
Intervention (2)
Intervention* [tiab] OR intervention stud* [tiab] OR psychosocial intervention* [tiab] OR "Reminder systems"[Mesh] OR medical informatics applications [tiab] OR patient education as topic OR health education/methods OR medication therapy management [tiab] OR patient centered care [tiab] OR client education [tiab] OR diabetes education [tiab] OR Physician-patient relation [tiab] OR self-management intervention [tiab] OR behaviour change [tiab] OR behavior change [tiab] OR interview* [tiab] OR health promotion [tiab] OR health coaching [tiab] OR computer systems [tiab] OR decision making [tiab] OR pharmaceutical service* [tiab] OR motivati* [tiab] OR disease management [tiab] OR "Electronic Health Records"[Mesh] OR counseling internet OR "counseling"[Mesh] OR telephone counseling [tiab] OR telephone [tiab] OR primary health care [tiab] OR video recording [tiab] OR multimedia [tiab] OR multi-media [tiab] OR therapy/computer-assist* [tiab] OR computer-assisted instruction [tiab] OR computer communication networks [tiab] OR user-computer interface [tiab] OR computer-based [tiab] OR cellular phone [tiab] OR mobile phone [tiab] OR remote consultation [tiab] OR world wide web [tiab] OR website [tiab] Limits: Title and abstract
Primary outcome (3)
Pharmaceutical regimen [tiab] OR Pharmaceutical treatment [tiab] OR Drug regimen [tiab] OR Stop$ treatment$ [tiab] OR abandon$ treatment$ [tiab] OR Patient compliance [tiab] OR Patient cooperation [tiab] OR Patient adherence [tiab] OR Patient non-compliance [tiab] OR Patient non compliance [tiab] OR Patient nonadherence [tiab] OR Patient Noncompliance [tiab] OR Patient Non-adherence [tiab] OR Patient non adherence [tiab] OR Medication adherence [Mesh] OR Medication compliance [tiab] OR Medication nonadherence [tiab] OR Medication non-compliance [tiab] OR Medication non compliance [tiab] OR Medication* [tiab] OR medication prescribed [tiab] OR Noncompliance [tiab] OR Medication non-adherence [tiab] OR Medication non adherence OR Medication Persistence OR medication taking OR Patient dropouts [Mesh] OR Patient Dropout* [tiab] OR Treatment Refusal [Mesh] OR Treatment Refus* [tiab] OR Refusal of Treatment [tiab] OR Patient Refusal of Treatment [tiab] Limits: Title and abstract excepted
In total, (1) AND (2) AND (3)
EMBASE
Population (1)
'non insulin dependent diabetes mellitus':ab,ti OR 'diabetes mellitus':ab,ti OR 'antidiabetic agent':ab,ti OR 'hypoglycemia':ab,ti OR 'glycosylated hemoglobin':ab,ti OR 'type 2 diabetes':ab,ti Limits: Title and abstract
Intervention (2)

'intervention study':ab,ti OR 'behavior':ab,ti OR 'social psychology':ab,ti OR 'reminder system':ab,ti OR 'medical informatics':ab,ti OR 'patient education':ab,ti OR 'education':ab,ti OR 'medication therapy management':ab,ti OR 'patient care':ab,ti OR 'doctor patient relation':ab,ti OR 'self care':ab,ti OR 'behavior change':ab,ti OR 'health promotion':ab,ti OR 'computer system':ab,ti OR 'patient decision making':ab,ti OR 'pharmacy':ab,ti OR 'disease management':ab,ti OR 'electronic medical record':ab,ti OR 'patient counseling':ab,ti OR 'information service':ab,ti OR 'primary health care':ab,ti OR 'videorecording':ab,ti OR 'multimedia':ab,ti OR 'computer assisted drug therapy':ab,ti OR 'computer network':ab,ti OR 'teleconsultation':ab,ti OR 'telephone':ab,ti OR 'mobile phone':ab,ti OR 'internet':ab,ti Limits: Title and abstract
Primary outcome (3)
'patient compliance':de,ab,ti OR 'treatment compliance':ab,ti OR 'patient cooperation':ab,ti OR 'patient adherence':ab,ti OR 'patient non-compliance':ab,ti OR 'patient non compliance':ab,ti OR 'patient nonadherence':ab,ti OR 'patient noncompliance':ab,ti OR 'patient non-adherence':ab,ti OR 'patient non adherence':ab,ti OR 'medication adherence':ab,ti OR 'medication compliance':ab,ti OR 'medication nonadherence':ab,ti OR 'medication non-compliance':ab,ti OR 'medication non compliance':ab,ti OR 'medication noncompliance':ab,ti OR 'medication non-adherence':ab,ti OR 'medication non adherence':ab,ti OR 'medication persistence':ab,ti OR 'medication taking':ab,ti OR 'treatment refusal':de,ab,ti OR 'treatment refusal':ab,ti OR 'refusal of treatment':ab,ti OR 'patient refusal of treatment':ab,ti OR 'drug dose regimen':ab,ti OR 'treatment withdrawal':ab,ti Limits: Title or abstract
In total, (1) AND (2) AND (3)
PsycINFO
Population (1)
diabetes OR diabetes mellitus OR Type 2 diabetes mellitus OR Type 2 diabetes OR non insulin dependent OR noninsulin dependent OR hypoglycemic agents OR hypoglycemia OR glycosylated hemoglobin Limits: Title or abstract
Intervention (2)
intervention study OR psychosocial intervention OR Reminder systems OR medical informatics applications OR patient education OR health education OR medication therapy management OR patient centered care OR client education OR diabetes education OR Physician-patient relation OR self management OR behaviour change OR behavior change OR interview OR health promotion OR health coaching OR computer systems OR decision making OR pharmaceutical service OR motivate OR Motivation OR disease management OR Electronic Health Records OR counseling internet OR counseling OR telephone counseling OR telephone OR primary health care OR video recording OR multimedia OR computer-assisted OR computer-assisted instruction OR computer communication networks OR user-computer interface OR computer-based OR cellular phone OR mobile phone OR remote consultation OR world wide web OR website OR Web Limits: Title or abstract
Primary outcome (3)
Patient compliance OR treatment compliance OR Patient cooperation OR Patient adherence OR Patient noncompliance OR Patient Non Compliance OR Patient Nonadherence OR Patient Noncompliance OR Patient nonadherence OR Patient Non Adherence OR Medication Adherence OR Medication Compliance OR Medication Nonadherence OR Medication noncompliance OR Medication Non Compliance OR Medication Noncompliance OR Medication nonadherence OR Medication Non Adherence OR Medication Persistence OR medication taking

OR treatment refusal OR Refusal of Treatment OR Patient Refusal of Treatment OR drug dose regimen OR treatment withdrawal Limits: Title or abstract
In total, (1) AND (2) AND (3)
Limits: Title or abstract
THE COCHRANE LIBRARY
Population (1)
Diabetes OR Diabetes mellitus OR type 2 diabetes OR Hypoglycemic Agents OR NIDDM OR T2DM OR T2D OR non insulin* depend* OR noninsulin* depend* OR MODY OR hypoglycemia OR glycosylated hemoglobin Limits: Trials; Title or abstract or keywords
Intervention (2)
Intervention* OR intervention stud* OR psychosocial intervention OR Reminder systems OR medical informatics applications OR patient education OR health education OR medication therapy management OR patient centered care OR client education OR diabetes education OR Physician-patient relation OR self-management OR behaviour change OR behavior change OR interview* OR health promotion OR health coaching OR computer systems OR physician-patient relation OR decision making OR pharmaceutical service* OR motivati* OR disease management OR Electronic Health Records OR counseling internet OR counseling OR telephone counseling OR telephone OR primary health care OR video recording OR multimedia OR multi-media OR computer-assist* OR computer-assisted instruction OR computer communication networks OR user-computer interface OR computer-based OR cellular phone OR telephone OR mobile phone OR remote consultation OR world wide web OR website OR Web Limits: Trials; Title or abstract or keywords
Primary outcome (3)
Pharmaceutical regimen OR Pharmaceutical treatment OR Drug regimen OR Stop* treatment* OR abandon* treatment* OR Patient compliance OR Patient cooperation OR Patient adherence OR Patient non-compliance OR Patient non compliance OR Patient nonadherence OR Patient Noncompliance OR Patient Non-adherence OR Patient non adherence OR Medication adherence OR Medication compliance OR Medication nonadherence OR Medication non-compliance OR Medication non compliance OR Medication* OR medication prescribed OR Noncompliance OR Medication non-adherence OR Medication non adherence OR Medication Persistence OR medication taking OR Patient dropouts OR Patient Dropout* OR Treatment Refus* OR Refusal of Treatment OR Patient Refusal of Treatment Limits: Trials; Title or abstract or keywords
In total, (1) AND (2) AND (3)
Limits: Trials; Title or abstract or keywords
CINAHL PLUS with Full Text
Population (1)
Hypoglycemia OR Hemoglobin A, Glycosylated OR Hemoglobin A OR Hypoglycemic Agents OR Diabetes Mellitus, Type 2 OR Diabetes Mellitus OR Diabetic Patients Limits: Title or abstract

Intervention (2)

Patient Education OR Health Education OR Diabetes Education OR Support, Psychosocial OR Reminder Systems OR Patient Record Systems OR Medical Informatics OR Computerized Patient Record OR Telephone Information Services OR Telephone OR Counseling OR Medication Management OR Health Information Management OR Health Information Management Service OR Patient Centered Care OR Nursing Home Patients OR Physician-Patient Relations OR Professional-Patient Relations OR Nurse-Patient Relations OR Disease Management OR Primary Health Care OR Health Care Delivery OR Home Health Care Information Systems OR Health Care Delivery, Integrated OR Health Services Needs and Demand OR Multimedia OR Computer Assisted Instruction OR Drug Therapy, Computer Assisted OR Therapy, Computer Assisted OR Signal Processing, Computer Assisted OR Decision Making, Computer Assisted OR Telephone Consultation OR Remote Consultation OR Nurse Consultants OR Internet OR World Wide Web

Limits: Title or abstract

Primary outcome (3)

Medication Reconciliation OR Treatment Outcomes OR Medication treatment OR patient abandonment OR Pharmaceutical regimen OR Pharmaceutical treatment OR Drug regimen OR Stop* treatment* OR abandon* treatment* OR Patient compliance OR Patient cooperation OR Patient adherence OR Patient non-compliance OR Patient non compliance OR Patient nonadherence OR Patient Noncompliance OR Patient Non-adherence OR Patient non adherence OR Medication adherence OR Medication compliance OR Medication nonadherence OR Medication non-compliance OR Medication non compliance OR Medication* OR medication prescribed OR Noncompliance OR Medication non-adherence OR Medication non adherence OR Medication Persistence OR medication taking OR Patient dropouts OR Patient Dropout* OR Treatment Refus* OR Refusal of Treatment OR Patient Refusal of Treatment

Limits: Title or abstract

In total, (1) AND (2) AND (3)

Limits: Title or abstract

CURRENT CONTENTS CONNECT (Social & Behavioral Sciences (SBS) --1998-present, Clinical Medicine (CM) --1998-present, Engineering, Computing & Technology (ECT) --1998-present**)**

Population (1)

TI= (Diabetes OR Diabetes mellitus OR type 2 diabetes OR Hypoglycemic Agents OR NIDDM OR T2DM OR T2D OR non insulin* depend* OR noninsulin* depend* OR MODY OR hypoglycemia OR glycosylated hemoglobin)

OR

TS= (Diabetes OR Diabetes mellitus OR type 2 diabetes OR Hypoglycemic Agents OR NIDDM OR T2DM OR T2D OR non insulin* depend* OR noninsulin* depend* OR MODY OR hypoglycemia OR glycosylated hemoglobin)

Limits: Articles; Topic

Intervention (2)

TS= (intervention stud* OR psychosocial intervention OR Reminder systems OR medical informatics applications OR patient education OR health education OR medication therapy management OR patient centered care OR client education OR diabetes education OR Physician-patient relation OR self-management OR behaviour change OR behavior change OR interview* OR health promotion OR health coaching OR computer systems OR physician-patient relation OR decision making OR pharmaceutical service* OR motivati* OR disease management OR

Electronic Health Records OR counseling internet OR counseling OR telephone counseling OR telephone OR primary health care OR video recording OR multimedia OR multi-media OR computer-assist* OR computer-assisted instruction OR computer communication networks OR user-computer interface OR computer-based OR cellular phone OR mobile phone OR remote consultation OR world wide web OR website) Limits: Articles; Topic
Primary outcome (3)
TS= (Pharmaceutical regimen OR Pharmaceutical treatment OR Drug regimen OR Stop* treatment* OR abandon* treatment* OR Patient compliance OR Patient cooperation OR Patient adherence OR Patient non-compliance OR Patient non compliance OR Patient nonadherence OR Patient Noncompliance OR Patient Non-adherence OR Patient non adherence OR Medication adherence OR Medication compliance OR Medication nonadherence OR Medication non-compliance OR Medication non compliance OR Medication* OR medication prescribed OR Noncompliance OR Medication non-adherence OR Medication non adherence OR Medication Persistence OR medication taking OR Patient dropouts OR Patient Dropout* OR Treatment Refus* OR Refusal of Treatment OR Patient Refusal of Treatment) Limits: Articles; Topic
In total, (1) AND (2) AND (3)
Limits: Articles; Topic
WEB OF SCIENCE
Population (1)
TI= (Diabetes OR Diabetes mellitus OR type 2 diabetes OR Hypoglycemic Agents OR NIDDM OR T2DM OR T2D OR non insulin* depend* OR noninsulin* depend* OR MODY OR hypoglycemia OR glycosylated hemoglobin) OR TS= (Diabetes OR Diabetes mellitus OR type 2 diabetes OR Hypoglycemic Agents OR NIDDM OR T2DM OR T2D OR non insulin* depend* OR noninsulin* depend* OR MODY OR hypoglycemia OR glycosylated hemoglobin) Limits: Articles; Topic
Intervention (2)
TS= (intervention stud* OR psychosocial intervention OR Reminder systems OR medical informatics applications OR patient education OR health education OR medication therapy management OR patient centered care OR client education OR diabetes education OR Physician-patient relation OR self-management OR behaviour change OR behavior change OR interview* OR health promotion OR health coaching OR computer systems OR physician-patient relation OR decision making OR pharmaceutical service* OR motivati* OR disease management OR Electronic Health Records OR counseling internet OR counseling OR telephone counseling OR telephone OR primary health care OR video recording OR multimedia OR multi-media OR computer-assist* OR computer-assisted instruction OR computer communication networks OR user-computer interface OR computer-based OR cellular phone OR mobile phone OR remote consultation OR world wide web OR website) Limits: Articles; Topic
Primary outcome (3)
TS= (Pharmaceutical regimen OR Pharmaceutical treatment OR Drug regimen OR Stop* treatment* OR abandon* treatment* OR Patient compliance OR Patient cooperation OR Patient adherence OR Patient non-compliance OR Patient non compliance OR Patient nonadherence OR Patient Noncompliance OR Patient Non-adherence OR Patient non adherence OR Medication adherence OR Medication compliance OR Medication nonadherence OR Medication non-compliance OR Medication non compliance OR Medication* OR medication prescribed OR

Noncompliance OR Medication non-adherence OR Medication non adherence OR Medication Persistence OR medication taking OR Patient dropouts OR Patient Dropout* OR Treatment Refus* OR Refusal of Treatment OR Patient Refusal of Treatment) Limits: Articles; Topic
In total, (1) AND (2) AND (3)
Limits: Articles; Topic

Supplementary-Table S_2: Data collection form

This data collection form was adapted from the data collection guide (intervention review – RCTs only) of the Cochrane Collaboration. We made a few modifications. We removed the study eligibility section because we used a separate form for article selection. We also replaced the risk of bias assessment section with the checklist and assessed the intervention studies' quality adapted from Methods for the development of NICE public health guidance (2nd edition) of April 2009. This checklist is more complete and allows for assessing both the internal and the external validity of intervention studies.

Review title or ID
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*
Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*
Notes:

1. General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/ abstract/ report that data are extracted from)*	
Report author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

2. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		

Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Notes:		

3. Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Aim of study		
Design *(e.g. parallel, crossover, cluster)*		
Unit of allocation *(by individuals, cluster/ groups or body parts)*		
Start date of study		
End date of study		
Total study duration		
Notes:		

4. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text** (pg & ¶/fig/table)
Total no. randomised *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Participant age in years, mean		
Participant Sex, male, N		
Particpant race/ethnicity		
Severity of illness		

Co-morbidities		
Other intervention received *(additional to study intervention)*		
Other relevant sociodemographics		
Notes:		

5. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Group name		
No. randomised to group *(specify whether no. people or clusters or total no. people in the studied groups for NRCTs)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of Intervention period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Notes:		

Intervention Group 2

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Group name		

No. randomised to group *(specify whether no. people or clusters or total no. people in the studied groups for NRCTs)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of Intervention period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Notes:		

6. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	

Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

Outcome 2

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Power		
Notes:		

7. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

	Description as stated in report/paper				**Location in text** *(pg & ¶/fig/table)*
Comparison					
Outcome					
Timepoint *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	

No. missing participants and reasons			
No. participants moved from other group and reasons			
Any other results reported			
Unit of analysis *(by individuals, cluster/groups or body parts)*			
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear		
Notes:			

Continuous outcome

	Description as stated in report/paper						**Location in text** *(pg & ¶/fig/table)*
Comparison							
Outcome							
Timepoint *(specify whether from start or end of intervention)*							
Post-intervention or change from baseline?							
Results	**Intervention (SMS group)**			**Comparison (telephone group)**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis *(individuals, cluster/ groups or body parts)*							

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	☐ ☐ ☐ Yes No Unclear		
Notes:			

8. Applicability

Have important populations been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	☐_☐ ☐ Yes No Unclear	
Is the intervention likely to be aimed at disadvantaged groups? *(e.g .lower socioeconomic groups)*	☐_☐ ☐ Yes No Unclear	
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	☐_☐ ☐ Yes No Unclear	
Notes:		

9. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies *(meeting our inclusion criteria)*		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

10. Checklist, assessment of methodological quality of intervention studies

Adapted from Methods for the development of NICE public health guidance (2nd edition) April 2009

Assessment criteria		**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
Section 1 : Population			
Is the source population well described? Description of country, type of healthcare system, setting, etc.?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		

Is the eligible population representative of the source population? Well defined recruitment? Important groups under-represented?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Do the selected participants represent the eligible population? Selection method well described? % of selected agreed to participate? Inclusion/exclusion criteria explicit and appropriate?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Section 2 : Allocation			
How was selection bias minimised? Allocation to exposure and comparison randomised? Truly random (++), pseudo-random (e.g. consecutive admissions) (+)? Was significant confounding likely (-) or not (+)?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were interventions and comparisons well described and appropriate?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Was the allocation concealed? Adequate allocation concealment would include centralised allocation or computerised allocation systems (++).	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were participants and/or investigators blind to exposure and comparison? If lack of blinding is likely to cause bias, score (-).	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Was the exposure to the intervention and comparison adequate?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Was contamination acceptably low?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were other interventions similar in both groups?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were all participants accounted for at the study conclusion?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Section 3 : Outcomes			
Were outcome measures reliable?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were all outcome measurements complete?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were all important outcomes assessed?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were outcomes relevant?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were follow-up times similar between groups?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		

Was follow-up time meaningful?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Section 4 : Analyses			
Were exposure and comparison groups similar at baseline? If not, were these adjusted?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Was the study sufficiently powered?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Were the analytical methods appropriate?	☐ ++ ☐ + ☐ − ☐ NR ☐ NA		
Section 5 : Summary			
Are the study results internally valid?	☐ ++ ☐ + ☐ −		
External validity?	☐ ++ ☐ + ☐ −		
++ = good, + = medium, - = low, NR= Not reported, NA= not applicable			

For the assessment of the items of checklist, one of five responses was possible:
(++): Indicates that for that particular aspect of study design, the study has been designed/ conducted in such a way as to minimize the risk of bias. In these conditions, we considered this item to be of good quality.
(+): Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design. In these conditions, we considered this item to be of medium quality.
(-): Should be reserved for those aspects of the study design in which significant sources of bias may persist. In these conditions, we considered this item to be of low quality.
Not reported (NR): Should be reserved for those aspects in which the study under review fails to report how they have/might have been considered.
Not applicable (NA): Should be reserved for those study design aspects which are not applicable given the study. (For example, random allocation would not applicable for prospective cohort studies).
In addition, the reviewers then award overall study quality by grading internal validity and external validity: Section 5: summary (internal validity and external validity). One of three responses was possible:
(++): All or most of the checklist items have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter. In these conditions, we considered the overall study quality to be good.
(+): Some of the checklist items have been fulfilled; where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter. In these conditions, we considered the overall study quality to be medium.
(-): Few or no checklist items have been fulfilled and the conclusions are likely or very likely to alter. In these conditions, we considered the overall study quality to be low.

Supplementary–Table S_3: Coding manual for behavior **change technique**

Modified from
De Bruin M, Viechtbauer W, Hospers HJ, Schaalma HP, Kok G. Variability in standard care quality of HAART-adherence studies: Implications for the interpretation and comparison of intervention effects. Health Psychology
and/or
De Bruin M, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact intervention effects in HAART adherence RCTs: A meta-analysis. Archives of Internal Medicine,

The orignal version of this coding manual was developped for behavioral interventions in patients with HIV. We made some minor modifications to use it for patients with type 2 diabetes.

General guidelines for using this manual for intervention coding
Please carefully read the taxonomy list before coding the intervention articles.
Suggestions for optimal coding:

- Read the [coding material] once before actual coding. Highlight relevant sections.
- Scan the different techniques presented in the coding table (last page).
- Start coding the relevant sections using the coding table. In case of any doubt between techniques, always turn to the description of the techniques presented in this document.
- Always make a note in the original material when coding a technique.
- There are 4 coding columns in the coding table. Two for first intervention contact, two for follow-up contacts. The white column to code techniques about which the coder is relatively sure, the grey section to note techniques about which the coder is unsure and may want to get back to later.
- Two techniques, i.e. Self-report of behavior and Electronic monitoring of behavior, are no actual behavioral change techniques. Coding of these techniques is informative but should not add to a score for quality of the intervention.

Tips: 1] Print this document with 2 pages per sheet, 1-sided, so you only have 3 pages with detailed techniques
2] Practice and discuss coding on 5 interventions before the studies selected for the review/meta-analysis

General guidelines for using the taxonomy as a tool for intervention development
The behavior change techniques described in this manual have been obtained from behavioral theories. Research has shown that, when applying these principles of change, certain parameters should be taken into account for optimal effectiveness (or to prevent boomerang effects). For an overview of these parameters, see:

Bartholomew LK, Parcel GS, Kok G, Gottlieb NH. *Planning health promotion programs: An Intervention Mapping approach*. First edition ed. San Fransisco: Jossey-Bass; 2006 (Chapter 7); for the relevant theories examine chapters 3 and 4 of this book, and "Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. *Health Psychol.* 2008;27 (3):379-387".

General guidelines for using this taxonomy when reporting standard and intervention care
This taxonomy and the taxonomy developed by Abraham and Michie (see previous reference) can be used to standardize descriptions of the active components of intervention and standard care delivered in research trials. For readers to understand better what is actually done in these trials, either use the BCT labels in these taxonomies and reference the taxonomy, or ensure that the description of standard and intervention care entails sufficient detail to allow coding with these taxonomies (i.e., explain what should change (i.e., determinants), through what principles this change should be accomplished, and how this was translated in practice).

General techniques

The three general techniques described below are techniques that can be an addition to specific behavior

change techniques (described on the following pages). If a general technique can be relevant for a specific technique, it will be mentioned in the definition of that specific technique. In case a general technique is applied to a specific technique, it should be scored in addition to the specific technique. There are cases where the general technique "2. Tailoring" can be applied to the intervention strategy as a whole, rather than to a specific technique:
2a: *Tailoring the whole intervention* protocol based on patient characteristics measured beforehand.
2b: *Tailoring the number of visits* to the need of a patient.
Such instances should be coded separately. **On the bottom of the coding table (final page), describe the use of these two techniques in the appropriate cells.**

1. Individualization
The provision of opportunities for learners to have personal questions answered or instructions paced according to their individual progress. Merely the assumption that there is the opportunity for the patient to ask questions because there is a 1-on-1 contact is not sufficient to score this technique: the patient must be either prompted to ask questions and/or it must be stated that instructions are paced according to individual progress and how it was paced.

2. Tailoring
Adapt the complete intervention strategy ***or*** specific intervention component(s) to previously measured characteristics of the patient. Score tailoring at the following different levels (see coding table, final page):

a) Macro-tailoring (group level): The intervention is adapted to certain pre-tested characteristics of the patients (e.g. a different intervention is applied to patients in different motivational stages; the type of intervention depends on the level of adherence; the materials have been made culturally sensitive).

b) Attention-tailoring (individual level): The amount of intervention contacts depends on the needs of the patient (e.g. someone with complex adherence problems would return after 4 weeks instead of 12 weeks).

c) Micro-tailoring (individual level): Specific behavior change techniques of the intervention strategy are tailored to the patient (e.g. action plan tailored to individual's lifestyle; risk information tailored to patient's risk status).

Note: All these techniques can be used in one intervention. For example, it is possible to *macro-tailor* the intervention on level of adherence (*group* tailoring) and to *attention-tailor* the number of intervention contacts and *micro-tailor* components of that intervention to characteristics of *individuals*.

3. Participation
The basic approach of the intervention, or the approach with regard to specific techniques, is to actively involve the patient in various stages of the intervention. For example, when identifying reasons for high adherence, or when determining the causes of non-adherence, how to change behavior, or which behavior change goals are feasible. An intervention description that states a dialogue should occur could be an instance of this technique, but there should be some specification on how participation was organized in relation to specific techniques. Participation logically leads to micro-tailoring of techniques, so participation and micro-tailoring may often look similar and can then be scored as either of the two, depending on which one is shown in the coding table under the relevant specific technique.
Note: To score this technique the patient must be prompted at various stages of the intervention to provide input or make decisions.

Specific techniques

Knowledge

1. Provide General Information
Basic information about type 2 diabetes, the medicines, the role of adherence, and how much adherence is enough.
Tailored: Information is tailored to the current level of knowledge and the needs of the patient (requires

first assessing this information/the need)

Individualization: The patient is prompted to have personal questions answered; includes **1-on-1 communication** between patient and professional (questions, clarification, and elaboration) (or confidential small-group sessions)

Note: Do ***not*** code here **Negative consequences** of target behaviors, instead code #3 "Risk communication."

Do ***not*** code here **Positive consequences** of target behaviors; instead code #15 "Persuasive argument."

All three techniques (1, 3, and 15) can be used concurrently.

2. Increase memory and/or understanding of transferred information

Use of **images**, **metaphors**, **rehearsing** or **repeating** information in own words, **and similar strategies** to help store in long-term memory. Also includes **group discussion** with an expert present; it is patient-**active** and includes patient prompts to ask questions, clarification, and elaboration. Merely group setting is ***not*** sufficient to be coded here.

Awareness

3. Risk communication

Information about costs/risks of action or inaction with respect to target behaviors. Also includes risk-communication strategies, such as scenario-based risk information and fear appeals.

Tailored: Communication/information is tailored to the patient's risk status (e.g. current behavior, clinical profile).

Note: Do ***not*** code here **positive consequences** of target behaviors; instead code #15 "Persuasive argument."

Note: Do ***not*** code here messages **not** including info on + or – outcomes; instead code #1 "General information."

4. Self-monitoring of behavior

Patient keeps a record of specified behaviors, e.g., a diary or a questionnaire of behavior over multiple time points between two intervention contacts (minimum 1 week to all days); or strategies were patients have to make notes of when and in what situation s/he experienced problems regarding the execution of the behaviors/goals set.

Note: Do ***not*** code here self-reports of behavior at one specific time-point, because self-report does not require previous self-monitoring and does not result in increased behavioral awareness of patient during period of behavioral execution; code instead #5 **"**Self-report of behavior."

Note: When #**4 Self-monitoring** includes reporting the outcomes to the professionals delivering the intervention, only code **#4 Self-monitoring. #5 Self-report** is purely for behavioral assessment and needs to be mentioned separately.

5. Self-report of behavior (Note: An *assessment* technique, not an actual *change* technique!)

Without prior instances of **self-monitoring** (#4), the patient is asked to **self-report** behavior (for at least the last 3 days). Also includes an electronic monitoring device that requires pressing a button at every intake.

Note: Different from technique #4 in that self-report does not involve reporting actively self-monitored data.

Note: Do ***not*** code **#5 Self-report** when it is part of **#4 Self-monitoring**. The behavioral assessment **#5 Self-report** must be mentioned separately.

6. Electronic monitoring of behavior (Note: An *assessment* technique, not an actual *change* technique!)

Patient is asked to monitor medication intake using an electronic monitoring device (e.g., **MEMS-cap, SMART-cap, SimPil, TrackCap, etc**) that automatically records "medication intake".

Note: Do ***not*** code here an electronic device that requires the patient to **press a button to register medication intake**; instead code #5 "Self-report of behavior".

Note: Code here use of a **SMART-cap** (or, **MEMS-*view* cap**) that is used for behavior monitoring, ***and*** also code #9 "Direct feedback on behavior."

7. Reflective listening: direct feedback of cognitions and emotions
Feedback of cognitions and emotions through reflective statements during **1-on-1** communication with the professional intended to increase awareness of own ideas, argumentation, emotions and relationships between these elements. Scoring requires explicit mention of this technique.
Note: Code here for **single MI-session**
Note: Do ***not*** code here **reflective** statements reflecting **ambivalence** between important **goals/values** in life and **current behavior**; instead code technique #14 "Reevaluation, self-evaluation."
Note: Do ***not*** code here **feedback of behavior**; instead code either #8 "Feedback: Delayed" or technique #9 "Feedback: Direct."

8. Feedback: Delayed feedback of behavior
a. Provide patient with an overview of recorded behavior; typically follows the previous setting of a desired/ ideal / recommended level of behavior. The behavior has to be recorded daily using either technique #4 Self-monitoring, #5 Self-report (pressing electronic button), or #6 Electronic monitoring. Score whether behavior was recorded **subjectively** (technique #4 & #5-electronic button) or **objectively** (#6).

b. Provide an objective reference for self-reported behavior – providing an objective reference for #5 Self-report (not electronic) over the ***last 3-7 days*** through feed back of Therapeutic Drug Levels (TDM).

Note: Do ***not*** code here self-report that is ***not*** combined with an objective reference; instead code only #5 "Self-report of behavior."
Note: Do ***not*** code here **a system/technology** enabling the patient to notice in daily life when medication has not been taken; instead code #9 "Feedback: Direct."
Note: Do ***not*** code here feedback that is linked to **previously formulated goals**; instead code #27 "Review of goals". Both techniques can be used concurrently.

9. Feedback: Direct feedback of behavior
Involves **a system/technology** designed to make people aware of their (lack of) behavioral performance (forgetting dose) **soon after** (<24 hours) **planned execution** (e.g., a dosette box with medication organized for every day of the week; a so-called SMART-cap with a display showing cap openings per day; a daily pill diary; a blister pack with days of the week). A medication diary or journal could be coded here.
Note: Do ***not*** code here a patient providing feedback with an overview of recorded data; instead code #8a "Feedback: Delayed, Overview."
Note: If this technique #9 is used to facilitate self-monitoring of behavior, also code #4 "Self-monitoring."

10. Feedback of clinical outcomes
Concerns feedback provided to the patient about clinical outcomes, i.e. glycemia and HbA1c.
Note: Do ***not*** code here when therapeutic drug levels are fed back to patients; instead code self-monitoring # 8b "Feedback: Delayed, Objective reference."

Social influence

11. Provide information about peer behavior ("Peer passive")
Information about what peers (i.e. people with type 2 diabetes using antidiabetic medication) do or think in relation to the target behavior or preparatory behaviors. This can be provided verbally or by using detailed case studies in text or in video. Focus is on providing social reference.
Note: Do ***not*** code here a **group setting** with peers; instead code #12 Opportunities for social comparison."
Note: Do ***not*** code here social norm of **important others**; instead code #13 "Mobilize social norm."
Note: Do ***not*** code here how to perform a behavior to increase self-efficacy; instead code #18 "Modeling."

12. Provide opportunities for social comparison ("Peer active")
Group sessions with peers in which discussion and social comparison can occur, not with the purpose of role modeling, but with the focus on providing social reference. Only score this technique in case discussion of adherence and/or preparatory behaviors is prompted, or experiences with these behaviors are shared

(personal stories). Med Adher Behavior Change Taxonomy 02/10/11

13. Mobilize social norm ("Important others")
Involves exposing the patient to the **social norm of important others** in relation to their execution of the target or preparatory behaviors. Important others may be family members, partners, friends, and also healthcare professionals (on the condition that they are important, i.e. valued and trusted experts).
Note: Do ***not*** code here social reference or comparison that explicitly focuses on peers instead of on important others; instead code #11 "Info about peer behavior (Peer passive)" or #12 "Social comparison (Peer active)."

Attitude

14. Reevaluation of outcomes, self-evaluation
Prompts to go through a process of (re)evaluation of outcomes of current behavior and alternative behaviors, and how these behaviors and outcomes relate to self-identity and/or important goals and values in life. Includes comparison of **desired behavior** versus **actual behavior** (e.g: Self-regulation theory), **reflections of ambivalence**/discrepancy between current behavior and goals/values, or assessment of the impact one's behavior has on one's environment (**environmental reevaluation**) with the aim to increase people's motivation.
Note: Code here for **single MI-session**
Note: Do ***not*** code here comparing **actual behavior** (following monitoring or self-report) with **previously formulated behavioral goals**; instead code #27 "Review of general and/or specific goals."

15. Persuasive argument, belief selection
Messages designed to strengthen positive beliefs about the outcome of the target behavior/behavior change and/or weaken negative beliefs about behavioral change. New beliefs may be introduced, or new information may be offered with the purpose to create new beliefs.
Tailored: Beliefs about the target behavior are explored after which the information is tailored to current belief structure.
Note: Do ***not*** code here argumentation to increase the efficacy beliefs; instead code #19 "Verbal persuasion."

16. Reinforcement on behavioral progress, provide contingent rewards
Techniques such as praise and encouragement that reinforce **behavioral progress**. Also includes material rewards and self-reward strategies, but the reward/incentive must be explicitly linked to the achievement of specified goals.
Note: Do ***not*** code here techniques that reinforce **motivational progress**; instead code #17 "Reinforcement on motivational progress, provide contingent rewards, affirmation."

17. Reinforcement on motivational progress, provide contingent rewards, affirmation
Includes praise and affirming remarks, as well as material rewards, following patient statements indicating movement towards increased motivation to change. Also includes reinforcement of efforts to actively participate in the intervention program.
Note: Code here for **single MI-session**
Note: Do ***not*** code here techniques that reinforce **behavioral progress**; instead code #16 "Reinforcement on behavioral progress, provide contingent rewards."

Self-efficacy / Skills

18. Modeling
Involves *showing* the patient step-by-step how to correctly perform a complex/challenging (set of) behavior (e.g. face-to-face demonstration by a professional to an individual, group, or class; video demonstration) with the objective to increase people's confidence in dealing with complex situations.

Note: Do ***not*** code here techniques that focus on providing social reference; instead code #11 "Provide information about peer behavior ("Peer passive")" or #12 "Provide opportunities for social comparison

("Peer active")."

19. Verbal persuasion (You can do it)
Persuasive messages designed to strengthen perceived efficacy/control beliefs related to execution of the target or preparatory behaviors. New beliefs may be induced and/or new information may be offered to create new control beliefs. This may take the form of tips or tricks for successful performance of behavior (i.e. often used strategies and Med Adher general tips from which the patient can choose); however, when tips are used, these must be relevant for the behavior of the individual at that moment.

Tailoring: Control beliefs about target behavior are explored after which the information delivered is tailored to the patient's current belief structure and/or personal situation and/or capabilities.

Note: Do ***not*** code here techniques that focus on persuasive arguments about outcomes of behavior; instead code #15 "Persuasive argument, belief selection."
Note: Do ***not*** code here presenting a list of ***general*** tips that may at some time be useful for the patient in the future; instead code #1"Provide general information."

20. Practice, guided practice
Prompt the patient to rehearse and repeat the behavior or preparatory behavior various times; or have the patient practice the behavior with the professional, after which they discuss the exercise and the professional provides feedback. Both these strategies are directed at increasing skill and confidence to execute target behaviors.

21. Plan coping responses
Determine actual or perceived barriers to adherence/preparatory behaviors, and ways to overcome these, in order to increase patients' confidence in being able to achieve these behavioral goals. Involves a focus on specific (anticipated or experienced) obstacles to performance. Barriers may include competing goals in specified situations, e.g., **prioritizing between goals** in favor of the target behavior; or "**problem solving**" if it is in relation to performance of behavior; or prompting the patient to perform **self-regulatory behaviors** (i.e. self-monitoring discrepancies between intended and actual behavior; and identifying strategies to overcome these).
Participation: Prompting the patient to both determine barriers ***and*** ways to overcome these; participation does ***not*** look like instructions.

Note: Code here for **single MI-session (participation)**
Note: Do ***not*** code here planning goal-directed behaviors that are ***not*** the result of specific barrier identification; instead code #26 "Specific goal setting."
Note: Do ***not*** code here techniques focused on maintenance of behavior after change occurred; instead code technique #32 "Formulate goals for maintenance of behavior."
Note: Do ***not*** code here general instructions on what the patient can do while no specific problems have yet arisen (sometimes part of information sessions/leaflets); instead code technique #1 "Provide general information."

22. Set graded tasks, goal setting
Movement towards complex/difficult goals is broken down into simple (but challenging) steps. The key aspect of this technique lies in planning to perform a sequence of preparatory actions that increases in difficulty over time, OR breaking down a complex task into manageable subtasks.
Participation: The patient determines whether or not the task is too complex and in which steps the task should be broken down to be manageable; participation does ***not*** look like instructions.
Note: Do ***not*** code here simply planning out a sequence of actions in detail, which does not follow from patients indicating the task is too complex/challenging; instead code #26 "Specific goal setting."

23. Reattribution training, external attribution of failure
Help patient reinterpret (previous) failure in terms of either unstable and/or changeable attributions; and previous successes in terms of stable and internal attributions. OR attribute failure to an external but controllable/avoidable factor, so that patient remains confident to attempt executing the behavior again.

Intention / Action Planning

24. General intention formation
Involves setting a general behavioral goal for the patient (e.g. take all medication on time) or formulating the desired outcomes of the behavior (e.g. HbA1c< 7%). Includes, as part of the action planning phase, explaining to patients that they are supposed to take all medications (on time) in order for treatment success, and that the goal of the treatment is to achieve a HbA1c< 7%"
Participation: Encourage the patient him/herself to set a general goal or make a behavioral resolution; participation does ***not*** look like instructions.

Note: Setting goals is part of **MI**, but scoring requires explicit mention of this technique.
Note: Do ***not*** code here explaining goals of treatment if it is not part of an "action planning phase"; instead code #1"Provide general information."
Note: Do ***not*** code here planning exactly what will be done or when the behavior/action sequence will be performed in order to accomplish high antidiabetic adherence/ HbA1c< 7%"; instead code #26 "Specific goal setting."
Note: Do ***not*** code here planning only the time of day for taking medication without any intentional expressions such as "I intend to take all medication on time"; instead code #25 "Develop medication intake schedule."
Note: Do **not** code here when patients are informed as part of the educational phase about the role of antidiabetic adherence in diabetes control and that the treatment should result in an HbA1c< 7%"; instead code #1 "Provide general information."

25. Develop medication intake schedule
Involves development of a schedule (time) of when to take the medication; basic planning of medication intake.
Tailored/ Participation: Patient is actively involved in determining when the medication intake is planned. May also be referred to as "tailored medication plan"
In writing: Medication schedule is written down for the patient to take home; can be pictures of medication/time of intake
Note: Do ***not*** code here planning preparatory behaviors or setting behavioral **goals** to change or facilitate adherence; code instead #26 "Specific goal setting."
Note: Code #30 "Use of cues" for **linking** of medication intake to daily routines or other cues.

26. Specific goal setting
Involves planning ***what*** the patient will do including, *at least*, a definition of the goal-directed behaviors that should result in **improved adherence**, **decrease in required efforts to adhere, or** HbA1c< 7% **(e.g., store spare doses of medicines at different locations)**. May include the specific contexts or situation in which the behavior will be performed (e.g. if-then plans: when leaving my house, I will take medication along). Includes the terms "Goal setting" and "Personal/action plan" since these ***do*** suggest formulation of goal-directed behaviors. Relates to action plans to increase or facilitate adherence on top of, or after, basic medication intake planning described in technique #25.
Participation: Encourage the patient to develop behavioral goals that best fit his/her lifestyle and intentions. Includes jointly developed or tailored action plans; participation does ***not*** look like instructions.
In writing: Goals can be ***written down*** in an action/personal plan for the patient to take home.
Note: Goal-directed behavior that has been further specified in terms of "**when, where, how, or with whom to act/if-then plans**" is an instance of **implementation intentions** and should ***also*** be coded as technique #30 "Use of cues;" however, this does ***not*** automatically imply #24 "General intention formation."
Note: Do ***not*** code here specific goal setting that is preceded by identifying important anticipated/experienced problems; instead code #21 "Plan coping responses."
Note: Do ***not*** code here medication intake planning that does not included formulation of sub-behaviors or preparatory behaviors that should lead to improved levels of adherence; instead code #25 "General intention formation."

27. Review of general and/or specific goals
Involves reconsideration of previously set goals or intentions following previous goal setting and an attempt to act on those goals
Participation: Encourage patient to reflect on previously set goals and intentions, and think about whether or not these still suffice; participation does ***not*** look like reflections from the professional.
Note: Do ***not*** code here comparison of **actual behavior** (following period of monitoring) to **desired behavior**; instead code #14 "Reevaluation of outcomes, self-evaluation."

28. Agree behavioral contract
Commitment to certain (behavioral) goals formulated in such a manner that non-adherence to these goals would have undesirable consequences for the patient, e.g. public commitment/signed contract. The patient must be aware at the moment of commitment/signing that these intentions will be evaluated in the future.
Note: Do ***not*** code here techniques do ***not*** involve public commitment or explicit signing; instead code written medication schedules as sub-technique #25 "Medication intake schedule/ in writing," or written personal/action plans as sub-technique #26 "Specific goal setting/ in writing."

Action control

29. Use of social support
Involves prompting the patient to think about how others could help change their behavior by providing assistance, (instrumental) social support, or emotional support; and planning to organize social support. Includes provision of support during the intervention, e.g. a "buddy" system or other forms of support
Note: If technique is part of planning a coping response because other people's behavior is perceived to be a key barrier to successful performance, code here ***and*** *also* code #21 "Plan coping responses."

30. Use of cues
Teach or stimulate patient to identify environmental prompts that can be used to remind them of the behavior/goals set. Includes times of day, alarm devices, stickers, doses of medication at visible location, particular contexts, or elements of contexts to help patient remember. Also includes **implementation intentions**, i.e., formulating specific goals in terms of "where, when, how, or with whom to act."

Note: If this technique includes **implementation intentions**, ***also*** code #26 "Specific goal setting"; however, this does ***not*** automatically imply use of #24 "General intention formation."
Note: **Cues** can also be used independent of #26 "Specific goal setting."
Note: Do ***not*** code here the mere use of the terms "goal setting" or "personal or action plan" or descriptions ***without*** clear illustration of this level of detail (i.e., environmental prompts or implementation intentions); instead code #26 "Specific goal setting."
Note: Do ***not*** code here **when people in the direct environment** are asked to help remember intake of medication; instead code #29 "Prompt use of social support."

31. Self-persuasion (I can do it)
Encourage/learn the patient to use self-motivating strategies to increase motivation and confidence **during periods of behavioral action**. This often takes the form of self-talk, i.e. prompt the patient to talk to themselves (aloud or silently) before and during planned behaviors to encourage and support action.

Maintenance

32. Formulate goals for maintenance of behavior
Includes at least the method described in technique #26 "Specific goal setting" but now focused on maintenance of behavior ***after*** change has occurred. May also include the method described in technique #24 "General intention formation", if that is focused on behavioral maintenance.
Participation: Encourage patient to develop goals to maintain behavior that best fit his/her lifestyle and intentions; participation does ***not*** look like instructions.

33. Relapse prevention
Following behavioral change, apply the same method as described in technique #21 "Plan coping

responses" but now focused on (long-term) maintenance of behavior.
Participation: Prompt the patient to determine both barriers **and** ways to overcome these; participation does ***not*** look like instructions.

Facilitation of behavior

34. Provide materials to facilitate behavior, or provide facilities to perform the behavior
Supportive materials are provided to the patients (e.g. reminder devices; dosette box; SMART-cap). Function of the material must be directly related to improvement of the target or preparatory behaviors, ***not*** to facilitate study-related behaviors (e.g. using a MEMS-cap to monitor adherence).

Note: Do ***not*** code here material that consists of written goals/instructions/medication schedule; instead code either sub-techniques #25 "Medication intake schedule/ in writing" or #26 "Specific goal setting/ in writing."
Note: Do ***not*** code here different materials (e.g. leaflet with information, video, workbook) used to deliver the intervention; instead list the materials used at the bottom of the table on the coding form.

35. Continuous professional support
Involves sending letters, making telephone calls, and opportunities for unplanned visits or follow up meetings after the major part of the behavior change intervention has been completed. Includes the opportunity for patients to contact their physician, nurse, or other intervention professional in case of problems

Note: Do ***not*** code here contacts that are an intrinsic part of the behavior change intervention.
Note: Do ***not*** code here contacts that are intended to serve as cues for behavior or as reminders of formulated goals; instead code technique #30 "Use of cues."
Note: Do ***not*** code here support that relates to side-effects; instead code technique #37 "Cope with side-effects."

36. Individualize regimen
Explicit mention that the regimen type (number of doses, number of pills per doses) is tailored to the needs of the patient.
Note: Do ***not*** code here strategies such as "tailored medication plan" that involve tailoring ***when*** medication is taken, but not the medication itself; instead code #25 "Develop medication intake schedule" and its sub-technique "Participation."

37. Cope with side-effects
Physician actively informs about side-effects and provides solutions for these (e.g., switching medicines or additional medication to suppress side-effects) OR prompts to contact healthcare professional between visits in case side-effects are experienced. Includes opportunity for patient to contact healthcare professional continuously for side-effects
Note: Do ***not*** code #35 "Continuous professional support" for continuous professional support related to side-effects.

38. Reduce environmental barriers
Activities aimed at reducing/solving problems that compete for attention with the target behavior, e.g. dealing with unemployment, legal issues, lack of food and housing, etc.

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**
Section 1 : Population																
Is the source population well described? Description of country, type of healthcare system, setting, etc.?	++	✓	✓		✓	✓	✓	✓		✓	✓	✓			✓	**10**
	+			✓					✓				✓	✓		**4**
	-															**0**
	NR															**0**
	NA															**0**
Is the eligible population representative of the source population? Well defined recruitment? Important groups under-represented?	++												✓			**1**
	+		✓		✓			✓								**3**
	-	✓		✓		✓	✓		✓	✓	✓	✓			✓	**9**
	NR													✓		**1**
	NA															**0**
Do the selected participants represent the eligible population? Selection method well described? % of selected agreed to participate? Inclusion/exclusion criteria explicit and appropriate?	++	✓	✓						✓	✓	✓					**5**
	+			✓	✓		✓					✓	✓		✓	**6**
	-					✓		✓								**2**
	NR													✓		**1**
	NA															**0**

continued on next page

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**
Section 2 : Allocation to intervention or comparison																
How was selection bias minimised? Allocation to exposure and comparison randomised? Truly random (++), pseudo-random (e.g. consecutive admissions) (+)? Was significant confounding likely (-) or not (+)?	++		✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	**11**
	+	✓								✓						**2**
	-															**1**
	NR															**0**
	NA			✓												**0**
Were interventions and comparisons well described and appropriate? (i.e enough for study to be replicated)	++					✓			✓	✓	✓	✓		✓	✓	**7**
	+	✓	✓	✓	✓		✓	✓					✓			**7**
	-															**0**
	NR															**0**
	NA															**0**
Was the allocation concealed? Adequate allocation concealment would include centralised allocation or computerised allocation systems (++).	++				✓	✓	✓	✓			✓	✓			✓	**7**
	+									✓						**1**
	-															**1**
	NR	✓											✓	✓		**3**
	NA		✓	✓					✓							**2**

continued on next page

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**
Were participants and/or investigators blind to exposure and comparison? If lack of blinding is likely to cause bias, score (-).	++												✓		✓	**2**
	+		✓		✓	✓			✓	✓		✓				**6**
	-						✓	✓			✓			✓		**5**
	NR	✓														**1**
	NA			✓												**0**
Was the exposure to the intervention and comparison adequate?	++	✓	✓	✓	✓	✓	✓		✓	✓	✓			✓		**10**
	+							✓				✓	✓		✓	**4**
	-															**0**
	NR															**0**
	NA															**0**
Was contamination acceptably low?	++	✓	✓	✓	✓	✓		✓	✓					✓	✓	**9**
	+										✓	✓	✓			**3**
	-									✓						**1**
	NR						✓									**1**
	NA															**0**
Were other interventions similar in both groups?	++															**0**
	+					✓										**1**
	-															**0**
	NR	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	**13**
	NA															**0**
Were all participants accounted for at the study conclusion?	++	✓	✓			✓			✓		✓	✓		✓	✓	**8**
	+							✓		✓			✓			**4**
	-				✓		✓									**2**
	NR			✓												**0**
	NA															**0**

continued on next page

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**
Section 3: Outcomes																
Were outcome measures reliable?	++	✓	✓		✓		✓				✓	✓	✓		✓	**8**
	+			✓		✓			✓							**3**
	-							✓		✓						**2**
	NR													✓		**1**
	NA															**0**
Were all outcome measurements complete?	++		✓		✓	✓	✓		✓	✓	✓	✓		✓		**10**
	+	✓						✓					✓	✓		**4**
	-															**0**
	NR			✓												**0**
	NA															**0**
Were all important outcomes assessed?	++	✓	✓		✓	✓		✓	✓		✓	✓		✓	✓	**10**
	+			✓									✓			**2**
	-						✓			✓						**2**
	NR															**0**
	NA															**0**
Were outcomes relevant?	++	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**14**
	+															**0**
	-															**0**
	NR															**0**
	NA															**0**
Were follow-up times similar between groups?	++	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**14**
	+															**0**
	-															**0**
	NR															**0**
	NA															**0**

continued on next page

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**
Was follow-up time meaningful?	++		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**13**
	+	✓														**1**
	-															**0**
	NR															**0**
	NA															**0**
Section 4 : Analyses																
Were exposure and comparison groups similar at baseline? If not, were these adjusted?	++	✓	✓		✓	✓		✓	✓		✓	✓		✓		**9**
	+			✓			✓			✓			✓		✓	**5**
	-															**0**
	NR															**0**
	NA															**0**
Was the study sufficiently powered?	++												✓			**1**
	+	✓	✓	✓	✓	✓	✓		✓		✓	✓		✓	✓	**11**
	-							✓								**1**
	NR									✓						**1**
	NA															**0**
Were the statistical methods appropriate?	++					✓			✓	✓	✓	✓		✓	✓	**7**
	+	✓	✓	✓	✓			✓					✓			**6**
	-															**0**
	NR						✓									**1**
	NA															**0**
Section 5 : Summary																
Are the study results internally valid?	++					✓			✓			✓			✓	**4**
	+	✓	✓		✓		✓				✓		✓	✓		**7**
	-			✓				✓		✓						**3**
External validity?	++															**0**
	+		✓		✓							✓	✓			**4**
	-	✓		✓		✓	✓	✓	✓	✓	✓			✓	✓	**10**

continued on next page

Supplementary-Table S_4: Assessment of the methodological quality of intervention studies

Assessment criteria	**Assessment**	Bogner/ 2010	Bogner/ 2012	Brennan*/ 2012	Farmer/ 2012	Heilser/ 2010	Lin/ 2012	Mehuys/ 2011	Nesari/ 2010	Phumipamorn/ 2008	Rosen/ 2004	Walker/ 2011	Odegard/ 2012	Zolfaghari/ 2012	Rothschild,/ 2013	**Total**

++ = good, + = medium, - = low, NR= Not reported, NA= not applicable

*The criteria related to blinding, concealment, and allocation groups were not applicable for Brennan's study. Consequently, we assessed the possibility of selection, information and confounding bias. We found that there were high possibility of selection biais and residual confounding bais.

Supplemental-Table S_5 : OAD adherence characteristics and intervention effects

Study *1. Authors* *2. Year*	**Instrument**	**OAD adherence characteristics** *1. Primary outcome* *2. Type of measure* *3. Validity's proofs* *4. Measure duration* *5. Score definition* *6. Variable form*	**Intervention** *1. Pre-interv.* *2. Post-interv.* *3. Follow-ups*	**Control** *1. Pre-interv.* *2. Post-interv.* *3. Follow-ups*	***P*-value**	**Study quality** *1. Internal* *2. External*
1. Rothschild 2. 2013	MEMS	1. No 2. Electronic 3. NR 4. 4 weeks 5. 0 (low)–100 (high) 6. ≥ 80% (adherents)	1. 44.4% 2. Graphic form 3. NA	1. 43.7% 2. Graphic form 3. NA	> 0.050	1. Good 2. Low
	4-item Morisky	1. No 2. Self-report 3. Yes 4. NR 5. 0 (low)–4 (high) 6. = 4 (adherents)	1. 30.6% 2. NR 3. NA	1. 28.2% 2. NR 3. NA	NR	
1. Zolfaghari 2. 2012	11-item SCDQ	1. Yes 2. Self-report 3. Yes 4. NR 5. 0 (low)–100 (high) 6. Continuous	1. 75.5% (14·3%) 2. 91.1% (11.6%) 3. NA	1. 73.3% (14.8%) 2. 94.7% (7.6%) 3. NA	0.037	1. Medium 2. Low
1. Odegard 2. 2012	MPR	1. Yes 2. Database 3. Yes 4. 48 weeks 5. 0 (low)–1 (high) 6. Continuous	1. 0.86 (0.17) 2. 0.90 (0.20) 3. NA	1. 0.84 (0.15) 2. 0.82 (0.20) 3. NA	0.01	1. Medium 2. Medium
1. Lin 2. 2012	APRD	1. Yes 2. Database 3. Yes 4. 48 weeks 5. 0 (low)–1 (high) 6. Continuous	1. 0.83 (0.19) 2. 0.85 (0.17) 3. NA	1. 0.83 (0.20) 2. 0.85 (0.18) 3. NA	> 0.050	1. Medium 2. Low
1. Farmer 2. 2012	EMC	1. Yes 2. Electronic 3. Yes 4. 12 weeks 5. 0 (low)–100 (high) 6. Continuous	1. Not measured 2. 77.4% (26.3%) 3. NA	1. Not measured 2. 69.0% (30.8%) 3. NA	0.044	1. Medium 2. Medium
	5-item MARS	1. Yes 2. Self-report 3. Yes 4. NR 5. 5 (low)–25 (high) 6. Continuous	1. 23.6 (2.3) 2. 23.6 (2.6) 3. NA	1. 23.6 (2.8) 2. 24.1 (1.6) 3. NA	0.200	
1. Bogner 2. 2012	MEMS	1. Yes 2. Electronic 3. Yes 4. NR 5. 0 (low)–100 (high) 6. ≥ 80% (adherents)	1. 35.9% 2. 62% 3. 65.2%	1. 42% 2. 34.1% 3. 30.7%	<0.001	1. Medium 2. Medium

continued on next page

Supplemental-Table S_5 : OAD adherence characteristics and intervention effects

Study *1. Authors* *2. Year*	**Instrument**	**OAD adherence characteristics**		**Intervention**	**Control**	***P*-value**	**Study quality**
		1. Primary outcome *2. Type of measure* *3. Validity's proofs*	*4. Measure duration* *5. Score definition* *6. Variable form*	*1. Pre-interv.* *2. Post-interv.* *3. Follow-ups*	*1. Pre-interv.* *2. Post-interv.* *3. Follow-ups*		*1. Internal* *2. External*
1. Walker* 2. 2011	MPR	1. No 2. Database 3. NR	4. 48 weeks 5. 0 (low)–100 (high) 6. ΔMPR≥ 20%	1. NR 2. NR 3. NA	1. NR 2. NR 3. NA	0.005	1. Good 2. Medium
	4-item Morisky	1. No 2. Self-report 3. Yes	4. NR 5. 0 (low)–4 (high) 6. > 2 (adherents)	1. 64.9% 2. NR 3. NA	1. 61.4% 2. NR 3. NA	> 0.050	
	1-item SDSCA	1. No 2. Self-report 3. Yes	4. 1 week 5. 0 (low)–7 (high) 6. ≥ 7 (adherents)	1. 72.1% 2. NR 3. NA	1. 74.6% 2. NR 3. NA	> 0.050	
1. Nesari 2. 2010	7-item SRQ	1. Yes 2. Self-report 3. Yes	4. NR 5. 0 (low)–100 (high) 6. Continuous	1. 61.1% (19.4) 2. 89.6% (10.0) 3. NA	1. 75.1% (15.6) 2. 78.0% (17.7) 3. NA	< 0.001	1. Good 2. Low
1. Heisler 2. 2010	NR	1. No 2. Self-report 3. Yes	4. 1 week 5. Missed dose/week 6. 0 missed (adherents)	1. 28% 2. 30% 3. NA	1. 34% 2. 37% 3. NA	0.540	1. Good 2. Low
1. Bogner 2. 2010	MEMS	1. Yes 2. Electronic 3. Yes	4. 2 weeks 5. 0 (low)–100 (high) 6. > 80% (adherents)	1. 34.5% 2. 62.1% 3. NA	1. 20.7% 2. 24.1% 3. NA	0.004	1. Medium 2. Low
1. Rosen 2. 2004	MEMS	1. Yes 2. Electronic 3. Yes	4. 4 weeks 5. 0 (low)–100 (high) 6. Continuous	1. 60% (NR) 2. 80% (NR) 3. 70% (NR)	1. 60% (NR) 2. 65% (NR) 3. 60% (NR)	0.017	1. Medium 2. Low
	1-item	1. No 2. Self-report 3. No	4. 4 weeks 5. 0 (low)–100 (high) 6. Continuous	1. 85% (NR) 2. 88% (NR) 3. 75% (NR)	1. 93% (NR) 2. 93% (NR) 3. 95% (NR)	0.520	

*Intervention effect was reported as odds ratio= 2.0, 95%CI= 1.2–3.2

NR= not reported; NA= not applicable; OAD= oral antidiabetic; SD= standard deviation; SCDQ= self-care diabetes questionnaire; MEMS= medication event monitoring system; EMC= electronic medication container; APRD= automated pharmacy refill data; MPR= medication possession ratio; SRQ= self-reported questionnaire; MARS= Medication Adherence Rating Scale; SRDC= self-reported drug compliance.

Supplementary Table S_6 : Sensitivity analyses, omitting each study one by one using random-effect model

Omitted study	Pooled effect	Statistic and *P*-value	Heterogeneity test
Bogner, 2010	0.15 [-0.11, 0.42]	Test for overall effect: Z = 1.13 (P = 0.26)	Heterogeneity: Tau^2 = 0.13; Chi^2 = 45.79, df = 8 (P < 0.00001); I^2 = 83%
Heisler, et al.	0.26 [-0.03, 0.54]	Test for overall effect: Z = 1.77 (P = 0.08)	Heterogeneity: Tau^2 = 0.15; Chi^2 = 45.31, df = 8 (P < 0.00001); I^2 = 82%
Nesari et al.	0.15 [-0.11, 0.42]	Test for overall effect: Z = 1.13 (P = 0.26)	Heterogeneity: Tau^2 = 0.13; Chi^2 = 45.46, df = 8 (P < 0.00001); I^2 = 82%
Walker et al.	0.19 [-0.11, 0.49]	Test for overall effect: Z = 1.26 (P = 0.21)	Heterogeneity: Tau^2 = 0.17; Chi^2 = 48.55, df = 8 (P < 0.00001); I^2 = 84%
Zolfaghari et al.	0.27 [-0.01, 0.54]	Test for overall effect: Z = 1.92 (P = 0.05)	Heterogeneity: Tau^2 = 0.14; Chi^2 = 45.31, df = 8 (P < 0.00001); I^2 = 82%
Odegard et al.	0.19 [-0.11, 0.48]	Test for overall effect: Z = 1.24 (P = 0.22)	Heterogeneity: Tau^2 = 0.17; Chi^2 = 47.43, df = 8 (P < 0.00001); I^2 = 83%
Lin et al.	0.24 [-0.06, 0.53]	Test for overall effect: Z = 1.58 (P = 0.11)	Heterogeneity: Tau^2 = 0.16; Chi^2 = 49.93, df = 8 (P < 0.00001); I^2 = 84%
Farmer et al.	0.26 [-0.01, 0.54]	Test for overall effect: Z = 1.87 (P = 0.06)	Heterogeneity: Tau^2 = 0.14; Chi^2 = 41.42, df = 8 (P < 0.00001); I^2 = 81%
Bogner 2012 et al.	0.14 [-0.12, 0.39]	Test for overall effect: Z = 1.06 (P = 0.29)	Heterogeneity: Tau^2 = 0.11; Chi^2 = 37.31, df = 8 (P < 0.0001); I^2 = 79%
Rothschild et al.	0.25 [-0.03, 0.53]	Test for overall effect: Z = 1.78 (P = 0.08)	Heterogeneity: Tau^2 = 0.15; Chi^2 = 47.26, df = 8 (P < 0.00001); I^2 = 83%
No omitting	0.21 [-0.05, 0.47]	Test for overall effect: Z = 1.56 (P = 0.12)	Heterogeneity: Tau^2 = 0.14; Chi^2 = 51.04, df = 9 (P < 0.00001); I^2 = 82%

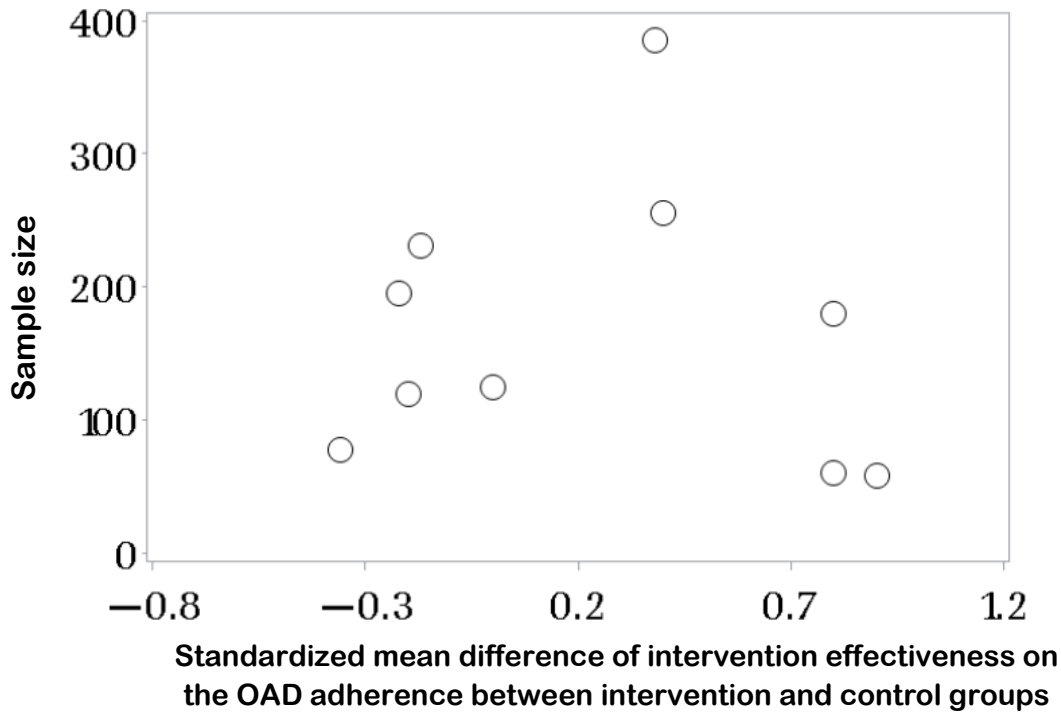
Meta-Analysis: Tests of Publication Bias

Egger Regression	t value	Probability
Egger OLS Regression	1.0483	0.3251

Begg Rank Correlation	z value	Probability
Begg Rank Correlation (Predictor=Variance)	0.2072	0.8359
Begg Rank Correlation (Predictor=Sample Size)	-0.2072	0.8359

Funnel Plot Regression	t value	Probability
Funnel Plot WLS Regression	-0.0661	0.9489

Trim and Fill	Publication Bias Present
Right Tail	No
Left Tail	No
Both Tails	No



Supplementary–Figure 1: Funnel plot of 10 studies included in the Meta-analysis

Supplementary-Table S_7: Impact of studies characteristics on pooled intervention effect size

Characteristics	N	Random-effects models			
		Hedges's g	95%CI	*p*-value	I^2
Mean age of participants					
≥ 60 years	4	0.17	-0.25 – 0.59		85%
< 60 years	6	0.24	-0.13 – 0.60		83%
Test for subgroup differences:				0.820	----
Type of OAD adherence measure					
subjective (self-report)	4	-0.03	-0.42 – 0.37		78%
objective (electronic or database)	6	0.36	0.07 – 0.64		76%
Test for subgroup differences:				0.130	----
Importance of OAD adherence as an outcome					
primary outcome	6	0.40	0.04 – 0.77		80%
secondary outcome	4	-0.04	-0.35 – 0.27		75%
Test for subgroup differences:				0.070	----
OAD adherence scale					
dichotomous	5	0.32	-0.10 – 0.74		85%
continuous	5	0.11	-0.25 – 0.47		82%
Test for subgroup differences:				0.470	----
Use of an intervention guide					
yes	6	0.31	-0.03 – 0.65		86%
no	4	0.04	-0.39 – 0.47		76%
Test for subgroup differences:				0.330	----
Duration of intervention period					
≥ 6 months	5	0.10	-0.16 – 0.37		72%
< 6 months	5	0.36	-0.19 – 0.92		89%
Test for subgroup differences:				0.410	----

N= number of studies; Hedges's g= bias-corrected standardized mean difference; CI= confidence interval; I^2= indicator of heterogeneity; OAD= oral antidiabetic drug