TITLE: Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with type 2 diabetes: systematic review of randomised trials

RUNNING HEAD: Monitoring and brief messaging to support medicines adherence

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Abstract 249

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ABSTRACT

Aims

We aimed to assess the impact of interventions promoting monitoring of medication use and brief messaging to support medication adherence in patients with Type 2 diabetes mellitus (DM), and investigate the extent of theory use to guide intervention development.

Methods

We systematically searched for controlled trials, published from 1990 onwards in Medline, Embase, CINAHL, PsycINFO and Cochrane library, evaluating interventions based on monitoring and brief messaging to support medication adherence in Type 2 DM patients, to examine their effectiveness.

Results

Eleven trials (comparing fifteen interventions) were identified. Only a small minority presented a low risk of bias. Three interventions were based on delivering brief messages, six on monitoring medication adherence, and six used both strategies. Messaging interventions included use of SMS text-messages, web-based feedback, and messages delivered through monitoring devices. Monitoring interventions included remote self-reporting of medication and telephone calls with healthcare staff. Improvements in medication adherence were observed in six interventions, although effect sizes were generally moderate. Only two interventions improved both adherence and clinical outcomes. A meta-analysis of five trials (eight interventions) combining monitoring and messaging strategies showed that the pooled difference in medication adherence between intervention and control was moderate and not statistically significant (standardised mean difference = 0.22 [95% confidence interval –0.05; 0.49]). Only four trials were based on explicit theoretical frameworks.

Conclusions

Although interventions based on messaging and monitoring have potential to improve medication adherence in Type 2 DM patients, evidence on their efficacy is limited and additional high-quality, theory-based research is needed.

INTRODUCTION

Up to 37% of patients with Type 2 diabetes mellitus (DM) stop using oral glucose lowering drugs within one year of starting treatment [1]. This is problematic as medication non-adherence is associated with poor clinical outcomes [2] and, in the United States, increased health care costs of up to one billion dollars [3].

Across all patient groups, evidence for effective interventions that can support patients in taking their medication is inconsistent and only a minority of trials, at low risk of bias, show improvement in adherence and clinical outcomes [4]. Similar findings have been found in systematic reviews focussing on adherence in patients with diabetes [5-9]. Increasingly, interventions are complex, addressing multiple factors, using behavioural, affective and provider focussed components [10]. Consequently, the costs of such interventions can be high involving face-to-face support and counselling.

A range of promising novel interventions utilising Internet or telephone-based support are now being identified for use in supporting diabetes self-management [11, 12]. They have the potential to deliver interventions at low-cost and wide-scale. However, since there are many possible intervention components that could be delivered in this way, it is important to identify which components of behaviour change interventions are most effective.

Information technology can be used to deliver brief automated messages through a variety of platforms including short message service (SMS) text messaging and interactive voice recognition [13, 14]. The potential for SMS messages to target a range of behavioural determinants of adherence to medication is clearly demonstrated in studies focussing on other long-term conditions [15-17]. Messages can be used to provide motivation, practical hints and tips about routines, cues to new behaviours, and social support [14, 18]. They can also be linked to monitoring of symptoms [19] or physiological parameters [20] to personalise messages and determine their timing.

Similarly, interventions that involve monitoring of medicines offer feedback to patients, can be used to target patient-level interventions at high-risk individuals and drive provider-focussed interventions [4, 21]. Aggregated data on prescribing and other direct patient monitoring techniques has potential to support adherence [19,

20], although individual-level feedback may be used. For example, contacting patients who did not fill their first prescription for a lipid lowering treatment increased medicine collection by 16%, with effects persisting for up to a year [22].

There is limited evidence for effectiveness of monitoring and messaging interventions for individuals with HIV, hypercholesterolemia and hypertension [14, 17, 20], including evidence of clinically relevant benefit from lower blood pressure.

The low-cost, scalable nature of brief messaging and monitoring interventions make them worth exploring to improve adherence in diabetes. There is evidence that specific beliefs and concerns associated with taking medication for diabetes may differ from beliefs and concerns held by people with other conditions [23]. To guide future research, the extent, content, and theoretical basis of interventions that have been tested in trials to date needs to be identified and characterised before further research to optimise existing interventions or develop new ones, and then and explore when, in what circumstances, and to what extent they are effective.

We aimed to examine the effectiveness of interventions for people with Type 2 DM in increasing medication adherence and improving glycated haemoglobin (HbA1c), that include (i) monitoring of medication adherence by self or others or (ii) delivery of brief messages intended to support taking medicines. We also aimed to assess the extent theory was used in the development of the included interventions.

METHODS

We carried out a systematic review of published controlled trials, including trials with non-randomised comparison groups. The review and its procedures were planned, conducted, and reported according to standard recommendations [24].

Inclusion Criteria

Interventions

Eligible interventions were those intended to support taking medicines containing either a monitoring or a brief messaging component, often as part of a complex and multi-component intervention. Monitoring of medication adherence was defined as repeated observations over time of the degree to which the person's behaviour corresponds with the recommendations agreed with a health care provider. Monitoring included monitoring of medications by self or others and as an explicitly stated intervention component. Brief messaging interventions were defined as messages delivered remotely, handled with algorithms or rule based systems, and where delivered by a clinician or other individual, followed a prescribed and scripted set of responses without requiring individual judgment about message content.

Comparisons

Trials were included where a usual care or control group received no intervention, or an alternative intervention that did not involve monitoring or brief messages.

Participants

We included trials targeted at adults with Type 2 DM who were prescribed any of the following medications: i) medication to reduce micro and macro-vascular risk, including oral or injectable drugs to reduce blood glucose levels, ii) medication to lower blood pressure, or iii) medication to lower lipids.

Outcomes

Trials using objective or subjective (patient-reported) measures as either primary or secondary outcome measures were included. Trials reporting a proxy measurement

of medication adherence (such as prescribing or dispensing data, or information about initial or subsequent medication) were included.

Exclusion Criteria

Trials were excluded if they i) had mixed populations of Type 1 and Type 2 DM where the findings from each population could not clearly be distinguished, ii) examined interventions based on blogs or social interaction, iii) were published before January 1990, or iv) were published only in the form of conference abstracts. We did not restrict inclusion by the type of professionals delivering the interventions or type of medications.

Searches

Searches were conducted in December 2014 in Medline, EMBASE, PsycInfo, CINAHL, and the Cochrane Register (online appendix 1). Search strategies were developed by modifying MeSH and keywords used in previously published systematic reviews [25-28].

Additional Searches

Relevant previously published reviews [29-32] were examined for additional trials. Forward and backward citation searches were conducted on all included articles.

Screening

Titles and abstracts were screened based on the participant, comparison and outcome inclusion and exclusion criteria outlined above. A subsequent review of the abstracts was carried out to identify i) trials of brief messaging interventions, and ii) trials evaluating monitoring.

Screening by titles and abstracts was conducted by SR, with a random sample of 10% also double screened by JMcS. Full text screening was independently undertaken by SR and AF. Where there was uncertainty, trials were discussed with the whole research team until agreement was reached.

Data extraction, quality assessment and use of theory

Data extraction, using structured forms, included: trial design, number of participants in each group, length of follow-up, key elements of the intervention, type of comparison group, adherence measures used, and impact of the intervention on medication adherence and clinical outcomes. We used the Cochrane collaboration's tool for risk of bias assessment [27].

The extent to which the trials used explicit theory was assessed using the coding scheme proposed by Michie and Prestwich [33]. The coding-scheme contains 19 items to assess whether a theory was mentioned, how theories were used in intervention design and in the selection of intervention techniques, how intervention evaluations tested theory and the implications of the results for future theory development.

Risk of bias and use of theory was independently appraised by two reviewers (SR and LMcG). We quantified reviewer agreement on trial 'risk of bias' and 'use of theory' criteria using the Cohen's kappa coefficient [34]. Disagreements were discussed until consensus was reached.

Data synthesis and analysis

The main results of the studies were summarized and classified into three groups: monitoring interventions, brief messages interventions and interventions including both components. Where possible, we pooled data to summarize the difference in change in medication adherence from baseline to the end of the trial between intervention and control groups. We anticipated that included trials would vary in their setting, intervention and design, so we used a random effects model to pool data [35]. The patient-reported measures for medication adherence also varied between trials so we used Cohen's method to calculate pooled effect sizes [36] based on standardized mean difference (SMD). We standardized scores where required so that higher scores indicated higher levels of adherence [36]. Where the standard deviation (SD) of the change between intervention and control group for an outcome was not provided, we derived them from baseline and final SDs, assuming a degree of correlation of 0.5 [37]. A sensitivity analysis was undertaken using different values

of correlation to determine whether the overall result of the analysis were robust to the use of imputed correlation coefficients. Heterogeneity was quantified by the I^2 statistic, where I>50% was considered evidence of substantial heterogeneity [38]. Publication bias was examined with funnel plots and presence of asymmetry tested with Begg [39] and Egger tests [40]. Meta-analyses were conducted with Stata, version 12.0. We set a threshold of P=0.05 to accept statistical significance.

RESULTS

Trial identification

The initial database search identified 1,833 references, of which 545 were duplicates (Fig. 1). Title and abstract screening identified 78 references (overall agreement between reviewers was 91%; *kappa* = 0.51). Following full text screening, 23 articles (including trial protocols and clinical trial registry entries) were included. Where a single trial was reported in more than one article, data from all those articles were combined. 11 separate trials examined the effectiveness of 15 separate interventions (four of the trials examined two interventions each). No additional eligible trials were identified as a result of the backward and forward searching.

FIGURE 1 ABOUT HERE

Characteristics of the interventions

Key characteristics of included interventions are reported in Table 1. Three interventions were based on brief messages (three trials [41-43]), six interventions based on monitoring (six trials [31, 44-52]), and six combined both strategies (four trials [31, 48-56]).

Interventions based solely on brief messages were delivered via SMS text-message [41-43], whereas the messages in those interventions combining messaging and monitoring strategies were delivered by SMS text-message [31, 48-50], and by web-based systems [53-56] or monitoring devices [51, 52]. Monitoring interventions included remote self-reporting of medication use [48-56] and telephone calls to patients from healthcare staff [44, 46, 47, 53-56].

All eleven trials identified examined the impact of the interventions on medication adherence. There was substantial heterogeneity in reporting of adherence as a trial outcome. Thirteen different outcome measures were reported (listed in Table 1 and online appendix 2). Most were patient-reported, but electronic monitoring and measures based on pharmacy data were also reported.

TABLE 1 ABOUT HERE

Risk of bias

Agreement was high in assessing risk of bias (kappa = 0.83). Only a small minority of the trials had a low risk of bias, and none were assessed as free of bias (Figs. 2-3), although all randomly allocated participants between groups.

Most frequent risks were related to blinding of participants and personnel to the interventions with blinding of outcome assessment considered inadequate in seven studies due to the use of self-reported measures of medication adherence.

FIGURES 2 & 3 ABOUT HERE

Effectiveness of the interventions on medication adherence

The impact of interventions on medication adherence is reported in Table 2. Most of the trials measured adherence to all types of medications prescribed to patients with type 2 DM (including diabetes specific medication but also other types of medication such as anti-hypertensive or antidepressant). Only a minority [31, 42, 44, 48-50] focused on specific types of medication, which included a combination of oral hypoglycaemic agents, antidepressant medications or medications for high cholesterol and hypertension.

The three trials exclusively based on messaging reported improved medication adherence, although the magnitude of the effects and their statistical significance were unclear [41-43].

Three of the six trials examining the impact of interventions exclusively based on monitoring observed improvements in medication adherence [44-46], whereas three trials found no effect [31, 47-52].

Two trials examining the impact of interventions including both messages and monitoring components observed a positive impact on medication adherence [31, 48-50, 53]. The remaining two trials [51, 52, 54-56] reported no significant differences in medication adherence between intervention and control groups.

Data from five trials with self-reported adherence measures [41, 46, 52, 53, 56] were pooled in a meta-analysis (Fig. 4). The five trials included eight comparisons assessing the impact of messages alone, or a combination of monitoring and messages. The pooled difference in change in adherence between intervention (n=754) and control groups (n=377) was estimated. The SMD between intervention and control groups was 0.22 (95% confidence interval –0.05 to 0.49) and not significant. Heterogeneity among the trials was high (I^2=77.3%). Interventions focused on the use of SMS text-messages appeared to be more effective than those interventions combining messages and monitoring strategies (0.95 [-0.13;2.03] vs 0.03 [-0.10;0.17], respectively). Sensitivity analysis confirmed that the overall result was robust to the use of imputed correlation coefficients. Egger and Begg tests for funnel plot asymmetry (Appendix 3) were significant (P=0.004 and P=0.003 respectively) although the analysis included a single trial [46] reporting large effects in medication adherence with a low number of participants.

FIGURE 4 ABOUT HERE

Effectiveness of the interventions on clinical outcomes

Three trials examined the impact of message interventions on clinically relevant outcomes (Table 2). One reported a difference in HbA1c between intervention and control groups of 5 mmol/mol (HbA1c=0.5%) [41]. In another [42], mean blood pressure, and total and LDL cholesterol concentrations improved, but not fasting plasma glucose, HbA1c or weight. In a third [43], the percentage of patients with less than 64mmol/mol (HbA1c<8.0%) increased over one year.

With the exception of one trial [31, 48-50], all the trials of interventions evaluating monitoring without messages reported clinically relevant outcomes. One [44],

reported that patients allocated to receive the intervention were more likely to achieve target HbA1c levels and improved mood. Another [46], reported significant improvements in HbA1c. A third [51, 52], reported that a low-intensity intervention (including only monitoring but not message reminders) significantly decreased HbA1c, but not blood pressure. Two other trials [45, 47] did not observe differences between the intervention and control.

Three trials evaluated the impact of interventions combining monitoring and messages on clinical outcomes. In one [53], no effect was observed on HbA1c levels. In another [54-56], consistent, modest improvements in HbA1c, lipidaemia, blood pressure, and 10 year coronary heart disease were observed, but between-group differences were not statistically significant on any of the measures. Finally another trial [51, 52] observed that the high-intensity intervention (including both monitoring and message reminders) significantly decreased HbA1c (-5 mmol/mol (0.4%); $P<0.05$), and systolic blood pressure (-6.05mmHg; $P<0.05$).

TABLE 2 ABOUT HERE

Use of theory in included studies

Only four out of the eleven trials [31, 41, 44, 48-50, 54-56] explicitly reported that the interventions used were based on theory. Each of the four trials reported using a different theoretical framework. One intervention [41] was based on the Health Belief Model [57]. Another primary-care trial [44] used an intervention development framework based on the Theory of Reasoned Action [58, 59]. Another primary-care trial included two interventions [54-56], both based on social cognitive theory, self-efficacy and the application of social-ecologic approaches to health issues [60]. A fourth trial based in community pharmacies [51, 52] used an intervention based on behavioural learning theory, drawn from wider theoretical perspectives on adherence [61].

Table 3 describes the extent to which the trials explicitly used theory in relation to a number of criteria [33]. Reviewer agreement on whether theory was used in the interventions was high (kappa= 0.97). Theory was explicitly mentioned in only four trials, and even then, there was variation in how thoroughly it was used (online appendix 4). For example, two of these four trials [31, 48-50, 54-56] presented evidence that the psychological constructs planned as targets for trial interventions were predictors of behaviour (criterion 2). None of the articles reported carrying out a mediational analysis of constructs or discussed the results in relation to theory.

TABLE 3 ABOUT HERE

DISCUSSION

This systematic review has identified six of eleven trials targeted at people with Type 2 DM, based on messaging or monitoring or both, that report small but statistically significant effect sizes for improvement in adherence when tested against a comparator. Pooled data from five trials using self-reported measures reported a small, non-significant standard mean difference in adherence. Only a small minority of the trials to-date have a low risk of bias and interventions are rarely based on explicit theoretical frameworks. The interventions used a wide variety of technical approaches including SMS text-messages, web based feedback; different ways of trying to change behaviour including prompts and informational messages; and different degrees of support from health care staff including remote self-reporting of medication and telephone calls from healthcare staff.

This is the first study to systematically examine and synthesise reports of trials examining the effectiveness of messaging and monitoring based interventions on adherence to medication in patients with Type 2 DM. Although this review has been carried out using rigorous methods, the findings are limited by the risk of bias in the findings of the majority of trials. The extent to which the interventions were developed and optimised for their setting is unclear, and the self-reported measures used may not be reliable [62]. Although tests for funnel plot asymmetry, intended to explore whether there might be missing trials, were positive, this may have been a chance finding resulting from the small number of interventions included in the analysis.

Previous systematic reviews have examined a number of different strategies to improve adherence to diabetes medication. Some interventions have focused on the use of educational approaches [5], others on interventions delivered by specific providers (e.g. pharmacists [7, 8] or nurses [63]) and others have used a broader approach, reviewing healthcare interventions to support medication adherence in patients with Type 2 DM [6, 10, 64]. In general these reviews offer a similar message to our own review: although some of the interventions led to improvements in

medication adherence and clinical outcomes, the results are inconsistent, and there is no evidence of superiority for any of the types of interventions tested.

Despite a strong rationale for exploring monitoring and messaging, particularly following evidence from management of individuals with hypertension, antiretroviral therapy for HIV and smoking cessation, [14, 17], it is clear that brief messaging interventions in diabetes have not been evaluated using well developed and characterised interventions, or with rigorous trial designs. Future trials would therefore benefit from formative work to develop interventions and embed them in clinical care pathways, the use of objective measures of medicine adherence [4], and work to further understand how to optimise the use of messaging to lead to changes in behaviour. Given the increasing evidence supporting the use of multifaceted interventions [4, 10], the aim of this type of research is however to deliver these interventions at sufficiently low cost that they can be delivered alongside, and further improve the effectiveness, of other interventions.

A wide range of self-reported outcome measures are used in the trials included in this review. However, evidence underpinning the validity and reliability for some is not strong [62]. For example, where individuals receive coaching in the need to take medications, there is a strong possibility of differential reporting of adherence to medication compared with individuals receiving usual care. Routinely collected data about prescribing can be used to monitor adherence and is non-intrusive, although care needs to be taken with the precise metric derived from the prescribing record [65]. Electronic medication monitoring [66, 67] is widely used, but can be seen as intrusive and is currently costly for routine use in clinical practice.

Some approaches to monitoring have strong face-validity, for example checking electronic records to see whether a patient continues to obtain prescriptions for medication and making contact to enquire the reason. However, automated systems to manage this task are not widely implemented despite research demonstrating its potential to reduce non-adherence in other conditions [22]. Although messages and

thresholds for making contact with patients would need to be optimised, adopting this approach could have immediate utility.

A challenge facing future intervention development in this area is the need for well-designed process evaluations to explore whether an intervention, designed to change behaviour and outcomes, is successful in changing the proposed mechanism through which change in behaviour could be brought about. There is an increasing recognition that progress in developing an evidence base for behaviour change interventions can be enhanced by applying theory, as it focusses attention on the mechanisms through which interventions might be effective [68]. As in the wider literature, we observe that the majority of interventions do not involve theory based development, and in those that have applied theory to develop the intervention, it was not use to refine the intervention, to examine process measures that might indicate effect, or refine it subsequently. We need to develop a better understanding of mechanisms of change and develop a basis for refining and developing better theory [69].

In conclusion, although interventions based on messaging and monitoring could appear promising to improve medication adherence in patients with Type 2 DM at low cost, good evidence is still scarce and more high-quality theory-based research is needed.

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CONFLICTS OF INTEREST

All authors confirm that they have no conflicts of interest

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TABLE 1. CHARACTERISTICS OF THE INTERVENTIONS IDENTIFIED IN THE SYSTEMATIC REVIEW

Author(s)/Country	Setting	Key elements of intervention	Theoretical model used	Comparison Group	Design	Medication adherence measure
1. Interventions based on brief messages to improve medication adherence						
Arora et al. (2013) [41]/ US	Hospital	Two text messages each day over 6 months containing educational/motivational content (1 per day), medication reminders (3 per week), healthy living challenges (2 per week) and diabetes trivia (2 per week). (*n* = 47)	"Health Belief Model" This model uses concepts of patients' perceptions of disease, in combination with their individual modifying factors and the cues to action they receive, to generate a likelihood of undertaking a health behaviour.	Usual care (*n* = 45)	Open-label two-arm RCT	Morisky Medication Adherence Scale (8 item self-report)
Brath et al. (2013) [42]/ Austria	Diabetes outpatient clinic	Electronic medication blisters and mobile phone used to automatically record information about timing and number of pills taken. SMS reminders sent when pills were not taken. (*n* = 53)	Not reported	Standard medication blisters and handwritten medication intake diaries (*n* = 53)	Cross-over trial	Electronic data in intervention condition, returned medication blisters for control
Shetty et al., (2011) [43]/ India	Not reported	SMS messages once every 3 days. Messages included advice on nutrition, physical activity, and healthy living, and reminders to follow medication prescriptions. (*n* = 110)	Not reported	Usual care (*n* = 105)	Two-arm pilot RCT	Questionnaire and diary

Author(s)/Country	Setting	Key elements of intervention	Theoretical model used	Comparison Group	Design	Medication adherence measure
2. Interventions based on monitoring to improve medication adherence						
Bogner et al. (2012) [44]/ US	Primary Care	Individualised program to monitor adherence and address factors contributing to non-adherence (e.g. depression, medication cost, side effects). Patients had in-person and telephone sessions with integrated care manager who collaborated with physician. (*n* = 88)	Model proposed by the authors, based on causes of medication non-adherence (including depression, chronic medical conditions, function, cognition, social support, cost of medications, side effects, and past experiences with medications). This model was initially based on the Theory of Reasoned Action.	Usual care (*n* = 92)	Two-arm RCT	Medication Event Monitoring System
Guldberg et al., (2011) [45]/ Denmark	Primary Care	Electronic feedback system for general practitioners which presented data on Type 2 diabetes population, allowing data to be used during individual consultations and to gain overview of quality of diabetes care. (*n* = 1317)	Not reported	Usual care (*n* = 1141)	Two-arm cluster RCT	Redeemed prescriptions
Nesari et al., (2010) [46]/ Iran	Community	Sixteen telephone calls by nursing student over 12 weeks. Each call assessed medication taking and other diabetes care behaviours (e.g. diet, exercise, foot care). Calls also	Not reported	Usual care (*n* = 30)	Two-arm RCT	Self-reported adherence questionnaire: 7 items about medication

Author(s)/Country	Setting	Key elements of intervention	Theoretical model used	Comparison Group	Design	Medication adherence measure
		included education and addressing non-adherence. (*n* = 30)				taking
Odegard et al., (2005) [47]/ US	Primary Care	Pharmacist care plan involving regular pharmacist-patient and pharmacist-provider communication about diabetes care progress. (*n* = 30)	Not reported	Usual care (*n* = 43)	Two-arm multi-clinic RCT	Self-reported 2-question recall (difficulty remembering and missed doses)
Vervloet et al., (2011, 2012, 2014) [31, 48-50]/ Netherlands	Community (pharmacies)	Real time medication monitoring dispenser (*monitoring component*).(n=48)	Not reported	Usual care (*n* = 57)	Three-arm RCT	Refill adherence
Wakefield et al., (2011, 2012) [51, 52]/ US	Primary Care	Responded to daily question (delivered and answered remotely): "have you taken all your medications as prescribed" (*monitoring component*), and one other question about diet, exercise, foot care or side effects. (*n* = 102)	Not reported	Usual care (*n* = 107)	Single-centre three-arm RCT	Self-reported medication taking scale (Morisky et al, 1986): 4 items addressing medication taking
3. Interventions combining monitoring and brief messages to improve medication adherence						
Fisher et al., (2013) [53]/ US	Community	*CASM group:* Web-based programme in which participants selected goals for diabetes self-management (including adherence) and monitored progress on the site (*monitoring component*).	Not reported	Leap Ahead: Computer-delivered diabetes support and education. (*n* = 81)	Three-arm practical RCT	Hill-Bone Compliance Scale (8 item self-report)

Author(s)/Country	Setting	Key elements of intervention	Theoretical model used	Comparison Group	Design	Medication adherence measure
		Participants received web-based feedback (*message component*) and four telephone calls over 12 week period to check progress. (*n* = 121)				
Fisher et al., (2013) [53]/ US	Community	*CAPS group:* CASM intervention (above) plus problem solving therapy to reduce diabetes distress. (*n* = 117)	Not reported	Leap Ahead: Computer-delivered diabetes support and education. (*n* = 81)	Three-arm practical RCT	Hill-Bone Compliance Scale (8 item self-report)
Glasgow et al., (2010, 2011, 2012), [54-56]/ US	Primary care	*CASM group:* Web-based programme in which participants selected goals for diabetes self-management (including adherence) and monitored progress on the site (*monitoring component*). Participants received web-based feedback (*message component*) and received periodic computer-based motivational and prompting telephone calls over 12 week. (*n* = 169)	Interventions based on the social-ecological theory. Their design was guided by a behavioural systems approach to diabetes self-management that applies validated behaviour change principles at patient, health care provider, and social-environmental levels.	Enhanced usual care: computer-based health risk appraisal feedback and recommended preventative care behaviours (*no monitoring*). (*n* = 132)	Three-arm practical RCT	Hill-Bone Compliance Scale (8 item self-report)
Glasgow et al., (2010, 2011, 2012), [54-56]/ US	Primary care	*CASM plus group:* CASM intervention (see above) plus two follow up calls from interventionist and invitation to attend three group	Interventions based on the social-ecological theory (see details above)	Enhanced usual care: computer-based health risk appraisal feedback	Three-arm practical RCT	Hill-Bone Compliance Scale (8 item self-report)

Author(s)/Country	Setting	Key elements of intervention	Theoretical model used	Comparison Group	Design	Medication adherence measure
		sessions about healthy eating, maintenance, and community diabetes resources (*n* = 162)		and recommended preventative care behaviours (*no monitoring*). (*n* = 132)		
Vervloet et al., (2011, 2012, 2014) [31, 48-50]/ Netherlands	Community (pharmacies)	Real time medication monitoring dispenser (*monitoring component*) and SMS reminders if dispenser not opened during time period agreed with pharmacist (*messaging component*). (*n* = 56)	Behavioural learning theory, which states that behaviour depends on stimuli or cues, either internal (thoughts) or external (environmental cues), which elicit certain behaviour. As such the desired behaviour can be learned and maintained by automation after sufficient repetition.	Usual care (*n* = 57)	Three-arm RCT	Refill adherence
Wakefield et al., (2011, 2012) [51, 52]/ US	Primary Care	Monitoring component plus prompts/messages about medications and other aspects of disease management (including behaviour and lifestyle). (*n* = 107)	Not reported	Usual care (*n* = 107)	Single-centre three-arm RCT	Self-reported medication taking scale (Morisky et al, 1986): 4 items addressing medication taking

RCT, randomized controlled trial; *n*= number of participants.

TABLE 2. MAIN FINDINGS OF THE IDENTIFIED TRIALS

Author(s)	Impact on medication adherence	Impact on clinical outcomes
1. Interventions based on brief messages to improve medication adherence		
Arora et al. (2013) [41]	Average increase of 0.9 points (11.3%) in patient-reported medication adherence in the intervention, whereas no significant differences were observed in the group receiving usual care.	Improved glycaemic control in the intervention group (higher reduction in mean HbA1c in the intervention than in the control group). After six months HbA1C level decreased by 12 mmol/mol (1.1%) in the intervention compared with 5 mmol/mol (0.6%) in the control group [Δ= 5 mmol/mol (0.5%); 95%CI –3 mmol/mol (-0.3%) to 13 mmol/mol (1.2%)].
Brath et al. (2013) [42]	Significantly better adherence to metformin in the intervention phase of the cross-over trial (*P*=0.04; effect size not reported), but no differences observed for the other three medications examined (Simvastatin, Rosuvastatin and Ramipril).	Statistically significant improvements observed in mean blood pressure (from 133/75 to 128/70 mmHg), and in total and LDL cholesterol concentrations (166 to 155, and 87 to 80mg dl^{-1}, respectively) but not in fasting plasms glucose, HbA1c, weight and HDL cholesterol.
Shetty et al., (2011) [43]	Unclear reported improvements in medication adherence in both intervention and control groups (effect sizes and group comparisons not reported).	The percentage of patients with <64 mmol/mol (<8.0%) and without hypertriglyceridemia increased significantly at the first year in the intervention group (from 31% to 55% and from 54% to 76%). Percentage with high LDL-C decreased significantly in both groups. There was no significant difference in the percentage of obesity among the patients in either group.
2. Interventions based on monitoring to improve medication adherence		
Bogner et al. (2012) [44]	After 12 weeks in the intervention group increased the proportion of patients with more than 80% adherence to oral hypoglycaemic agent (from 37% to 65%; *P*<0.001) and to antidepressant medication (from 30% to 61%; *P*<0.001), whereas no differences were observed in the control group.	Patients who received the intervention were more likely to glycated haemoglobin<53 mmol/mol (<7%)(intervention 60.9% vs usual care 35.7%; *P*<0.001) and remission of depression (PHQ-9 score <5: intervention 58.7% vs usual care 30.7%; *P*<0.001) in comparison with patients in the usual care group at 12 weeks.

Author(s)	Impact on medication adherence	Impact on clinical outcomes
Guldberg et al., (2011) [45]	Patients the intervention group more often redeemed recommended prescriptions than patients in the control group (oral antidiabetic treatment, 32.8% vs. 12.0%; insulin treatment, 33.8% vs. 12.4%; lipid-lowering medication, 38.3 vs. 18.6%; blood pressure medication, 27.6% vs. 16.3%, all differences being statistically significant).	No differences were observed between the intervention and control group after the intervention in the two outcome measures included in the trial (glycated haemoglobin and serum cholesterol).
Nesari et al., (2010) [46]	8.44% increase in patient reported medication adherence score in the intervention group, whereas no statistically significant differences were observed in the control group.	Significant difference in HbA1c between the groups after 12 weeks (experimental group: 53 mmol/mol (7.0%); control group: 71 mmol/mol (8.6%); *P*<0.001).
Odegard et al., (2005) [47]	No significant differences between the intervention and control group were observed in medication adherence.	No differences in HbA1c between groups over the 12-month period (*P*=0.61). A reduction in HbA1c was noted for both groups over time compared with baseline (*P*=0.001).
Vervloet et al., (2011, 2012, 2014) [31, 48-50]	No significant differences between the intervention and control group were observed in medication adherence.	Clinical outcomes not examined
Wakefield et al., (2011, 2012) [51, 52]	No significant differences between the intervention and control group were observed in medication adherence.	The low-intensity intervention (including only monitoring but not message reminders) significantly decreased HbA1c (-4 mmol/mol (-0.4%), *P*<0.05), but not blood pressure.
3. Interventions combining monitoring and brief messages to improve medication adherence		
Fisher et al., (2013) [53]	*CASM group:* No significant differences between the *CASM* and control group were observed in medication adherence.	*CASM group:* No significant time or group effects observed for the only intermediate outcome examined (HbA1c).
Fisher et al., (2013) [53]	*CAPS group:* Higher improvement in medication adherence that the CASM and the control group (*P*<0.05)	*CAPS group:* No significant time or group effects observed for the only intermediate outcome examined (HbA1c).

Author(s)	Impact on medication adherence	Impact on clinical outcomes
Glasgow et al., (2010, 2011, 2012), [54-56]	*CASM group*: No significant differences between the intervention and control group were observed in medication adherence.	*CASM group*: Consistent, modest improvements in all the clinical outcomes (body mass, HbA1c, lipidemia, blood pressure, 10 year coronary heart disease) across the 12-month period in the intervention groups, but between-group differences were not statistically significant on any of the measures.
Glasgow et al., (2010, 2011, 2012), [54-56]	*CASM plus group*: No significant differences between the intervention and control group were observed in medication adherence.	*CASM plus group*: Consistent, modest improvements in all the clinical outcomes (body mass, HbA1c, lipidemia, blood pressure, 10 year coronary heart disease) across the 12-month period in the intervention groups, but between-group differences were not statistically significant on any of the measures.
Vervloet et al., (2011, 2012, 2014) [31, 48-50]	After one year medication adherence in the intervention group was significantly higher than in the control group (79.5% vs. 64.5%; *P*<0.001) and showed a significant improvement from baseline (+16.3%; *P*<0.001).	Clinical outcomes not examined
Wakefield et al., (2011, 2012) [51, 52]	No significant differences between the intervention and control group were observed in medication adherence.	Higher improvements in glycaemic control and blood pressure in the two intervention groups than in the control group.

HbA1c, glycated haemoglobin; mmHg, millimetre of mercury; Δ, between group difference; CI, confidence interval ; LDL-C, low density lipoprotein cholesterol;

TABLE 3. DEGREE OF USE OF THEORY IN THE DEVELOPMENT OF THE INTERVENTIONS*

Criterion	Description	Number of trials for which there is some evidence that this criterion is satisfied (N=11)
1. Theory/model of behaviour mentioned	Models/theories that specify relations among variables, in order to *explain* or *predict* behaviour are mentioned, even if the intervention is not based on this theory.	4
2. Targeted construct mentioned as predictor of behaviour	Evidence that the 'targeted' construct that the study intervention is hypothesized to change is presented within the introduction or method	2
3. Intervention based on single theory	The intervention is based on a single theory (rather than a combination of theories or theory predictors).	2
4. Theory used to select recipients for the intervention	Participants were screened/selected based on achieving a particular score/level on a theory-relevant construct.	0
5. Theory used to select/ develop intervention techniques	The intervention is explicitly based on a theory or combination of theories and predictors.	4
6. Theory used to tailor intervention techniques to recipients	The intervention differs for different sub-groups that vary on a psychological construct (e.g., stage of change) at baseline.	0
7. All intervention techniques are explicitly linked to at least one construct	Each intervention technique is explicitly linked to at least one theory-relevant construct.	1
8. At least one, but not all, of the intervention techniques are explicitly linked to at least one theory-relevant construct	At least one, but not all, of the intervention techniques are explicitly linked to at least one theory-relevant construct.	2
9. Group of techniques are linked to a group of constructs	A cluster of techniques is linked to a cluster of constructs.	0
10. All theory-relevant constructs are explicitly linked to at least one intervention technique	Every theoretical construct within a stated theory (see item 5) is linked to at least one intervention technique.	1
11. At least one, but not all, of the theory relevant constructs are explicitly linked to	At least one, but not all, of the theoretical constructs within a stated theory are linked to at least one intervention technique.	2

at least one intervention technique		
12. Theory-relevant constructs are measured	(a) At least one construct of theory mentioned in relation to the intervention is measured post-intervention.	1
13. Quality of measures	At least one of the measures of theory relevant constructs had some evidence for their reliability.	0
	At least one of the measures of theory relevant constructs have been previously validated	0
	The behaviour measure had some evidence for its reliability	3
	The behaviour measure has been previously validated.	3
14. Randomization of participants to condition	Do the authors claim randomization?	4
	Is a method of random allocation to condition described (e.g., random number generator; coin toss).	4
	Was the success of randomization tested?	4
	Was the randomization successful (or baseline differences between intervention and control group statistically controlled)?	3
15. Changes in measured theory-relevant constructs	The intervention leads to significant change in at least one theory-relevant construct/ predictor (vs. control group) in favour of the intervention.	0
16. Mediational analysis of construct(s)	Any evidence of hypothesised mediating variable or change in hypothesised mediating variable predicting dependent variable?	0
17. Results discussed in relation to theory	Results are discussed in terms of the theoretical basis of the intervention	0
18. Appropriate support for theory	Support for the theory is based on appropriate mediation OR refutation of the theory is based on obtaining appropriate null effects	0

19. Results used to refine theory	The authors attempt to refine the theory upon which the intervention was based by either adding or removing constructs to the theory, or specifying that the interrelationships between the theoretical constructs should be changed	0

* Extent to which the interventions are theory-based, examined by using the theory coding scheme developed by Michie et al [33].Information reported only for the four trials that reported the use of a theoretical model for the development of the intervention(s) (item 1 = yes).
DV = dependent variable; IV= independent variable; HBM =Health Belief Model; SCT =Social Cognitive Theory; TPB =Theory of Planned Behaviour

FIGURE LEGENDS

Figure 1. Flowchart of articles included at each stage of the screening process

Figure 2. Cochrane summary risk of bias for trials of monitoring of medication use and brief messaging interventions to promote medication adherence for patients with type 2 diabetes (n = 11).

Figure 3. Cochrane individual risk of bias for trials of monitoring of medication use and brief messaging interventions to promote medication adherence for patients with type 2 diabetes (n = 11)

Figure 4. Standardised mean difference in size of effect of intervention compared with “no treatment” for patient-reported adherence to diabetes medication. SMD, standardized mean difference; CI, confidence interval; N, number of participants; SD, standard deviation.