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Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus (Review)

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[Intervention Review]

Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus

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ABSTRACT

Background

Research suggests adherence to treatment recommendations is low. In type 2 diabetes, which is a chronic condition slowly leading to serious vascular, nephrologic, neurologic and ophthalmological complications, it can be assumed that enhancing adherence to treatment recommendations may lead to a reduction of complications. Treatment regimens in type 2 diabetes are complicated, encompassing life-style adaptations and medication intake.

Objectives

To assess the effects of interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus.

Search methods

Studies were obtained from searches of multiple electronic bibliographic databases supplemented with hand searches of references.

Selection criteria

Randomised controlled and controlled clinical trials, before-after studies and epidemiological studies, assessing changes in adherence to treatment recommendations, as defined in the objectives section, were included.

Data collection and analysis

Two teams of reviewers independently assessed the trials identified for inclusion. Three teams of two reviewers assessed trial quality and extracted data. The analysis for the narrative part was performed by one reviewer (EV), the meta-analysis by two reviewers (EV, JW).

Main results

Twenty-one studies assessing interventions aiming at improving adherence to treatment recommendations, not to diet or exercise recommendations, in people living with type 2 diabetes in primary care, outpatient settings, community and hospital settings, were included. Outcomes evaluated in these studies were heterogeneous, there was a variety of adherence measurement instruments. Nurse led interventions, home aids, diabetes education, pharmacy led interventions, adaptation of dosing and frequency of medication taking showed a small effect on a variety of outcomes including HbA1c. No data on mortality and morbidity, nor on quality of life could be found.

Authors' conclusions

Current efforts to improve or to facilitate adherence of people with type 2 diabetes to treatment recommendations do not show significant effects nor harms. The question whether any intervention enhances adherence to treatment recommendations in type 2 diabetes effectively, thus still remains unanswered.

PLAIN LANGUAGE SUMMARY

Interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus

Twenty-one studies assessing interventions to improve adherence to treatment recommendations, not to diet or exercise, in people with type 2 diabetes in different settings (outpatients, community, hospitals, primary care) were included. There were many outcomes evaluated in these studies and a variety of adherence measurement instruments was used. Nurse led interventions, home aids, diabetes education and pharmacy led interventions showed a very small effect on some outcomes including metabolic control. No data on mortality or morbidity, nor on quality of life could be found.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

Type 2 diabetes mellitus is one of the most common chronic diseases. The number of people with type 2 diabetes mellitus is continuously increasing worldwide. Six percent of the population of the world suffers from this disease, and only half of them have been diagnosed (Amos 1997). Strict metabolic control (for micro-vascular related outcomes) and blood pressure control (for micro- and macrovascular related outcomes) seem to be of importance in order to prevent vascular complications: macro- and micro-vascular disease being the most substantial diabetes-related causes of morbidity and mortality (Kinmonth 1999; UKPDS 33 1998; UKPDS 34 1998; UKPDS 34 1998; UKPDS 38 1998; Vermeire 1999; Wens 1999).

The potential benefits of any adequate treatment though are not similar for all cases. The risk of micro-vascular complications increases with the plasma glucose concentration and the duration of diabetes, while the risk of macro-vascular disease depends on age, gender, genetic factors, and life-style (for example nutrition, exercise, smoking), as well as hyperglycaemia (Goyder 1998). Once diabetes has been diagnosed, diabetes patients are confronted with the need for life-style adaptation, for example, weight reduction, adapted nutrition and more exercise. A treatment with oral hypoglycaemic agents or insulin is often unavoidable. In order to reduce diabetes-related complications, blood pressure and blood lipids control as well as foot care are necessary. All this requires a substantial degree of treatment adherence from patients. Patient compliance or patient adherence to treatment has been acknowledged, irrespective of the type of disease, to be a major problem in health care, involving consumers and health care providers equally. Not one in two patients adheres to treatment to health care recommendations as proposed (Vermeire 2001).

Low compliance

Low compliance to prescribed medical interventions is an ever present and complex problem, especially for patients with a chronic illness. With increasing numbers of medications and other medical interventions shown to do more good than harm when taken or implemented as prescribed, low compliance is a major problem in health care. Three decades have passed since the start of compliance research. The enormous amount of quantitative research undertaken is of variable methodological quality, with no gold standard for the measurement of compliance and it is often not clear which type of non-compliance is being studied. Medical non-compliance imposes a considerable financial burden upon modern health care systems. This burden is estimated to be 100 billion dollars each year in the USA (Donovan 1992; Donovan 1995; Haynes 1997; Morris 1992). Compliance to treatment is a key link between process and outcome in medical care. Therefore poor compliance may have a major impact on clinical outcome.

From compliance to concordance

Compliance is a word with negative connotations. It suggests yielding and submission to prescriptions of doctors. In the context of health care, compliance has been defined as the extent to which a person's behaviour in terms of taking medication, following diets, or executing life-style changes coincided with medical or health advice. Compliance can also be viewed in terms of the results of taking medication: the number of doses not taken or taken incorrectly that jeopardize the therapeutic outcome or the point below which the desired therapeutic result is unlikely to be achieved. These are process-oriented definitions. Outcome-oriented definitions differ from them because the emphasis is on the end-result.

The process of seeking, receiving and following treatment and advice has many stages and many opportunities for non-compliance. Different types of non-compliance include: delay in seeking care, non-participation in health programmes, breaking of appointments and failure to follow doctors' advice. Other types can be distinguished: receiving a prescription, but not having it picked up at a pharmacy, taking an incorrect dose, taking the medication at wrong times, forgetting one or more doses of the medication or stopping the treatment too soon. Furthermore, compliance may be intentional or unintentional. There is something morally and psychologically flawed in the very concept of compliance. Perhaps non-compliance may be no more deviant than compliance. Non-compliance can be defined as a person's informed decision not to adhere to a therapeutic treatment. The backbone of the concordance model is the patient as a decision maker, and a cornerstone is professional empathy. Concordance indicates the extent to which what the patient thinks about what is asked from him matches what the health care-giver thinks the patient actually does. The term adherence has been proposed as an alternative to compliance and is growing in popularity. It is suggested that this term incorporates the broader notions of concordance, cooperation and partnership.

Description of the intervention

Compliance research

The lack of a valid method for measuring compliance has itself been a major barrier to compliance research. There are a number of traditional measures of patients' compliance in taking medication, including both direct and indirect measures. Direct measures involve the detection of a chemical in a body fluid. However, these are not available for all medications. In addition, they may not account for the variability of pharmacokinetic factors of medications and individuals. Direct observation is only possible in restricted situations. Indirect measures are more frequently used. They include process measures such as interviews, diaries, tablet counts, electronic devices, prescription filling dates and therapeutic and preventive outcome measures. Each of these has drawbacks. Patients can improve for reasons other than following the prescribed regimen and a person's condition can deteriorate or remain stable even when the medications are taken as prescribed.

To date, none of the suggested explanations of compliance or non-compliance has accounted for more than a modest part of the observed variation in compliance. Almost 200 different doctor-, patient- and encounter-related variables have been studied but none of them has been found to be consistently related to compliance or to be fully predictive. Researchers designing clinical trials to evaluate a medical therapy may do so under two different settings: (i) under ideal experimental circumstances with treatments taken in the manner prescribed, or (ii) under the circumstances pertaining to usual medical practice. However, a true difference in efficacy may be diluted by differential compliance between treatment groups. The difficulty in measuring compliance hinders attempts to evaluate methods for enhancing compliance. Methods that have been investigated include short-term regimens, fewer doses per day, lower medication costs, easy-to-use packaging, reminders, tailoring information for the individual patient, patient education, and patient satisfaction measurement. It is also important to assess the impact of side-effects on compliance to that particular treatment. Non-compliance with scheduled appointments may also have important effects on health outcomes. In order to enhance this type of compliance, different patient-related, medical-encounter-related and care delivery system interventions have been assessed. Because one of the most commonly advocated ways to enhance compliance is the improvement of the doctor-patient relationship, different aspects have been highlighted and assessed (Vermeire 2001).

Other issues that have to be addressed are self-management and self-care. These terms focus on the fact that the patient himself takes care of a series of aspects of the medical treatment, in this case of the diabetes treatment. These can be, for example, the self-monitoring of blood glucose and the adaptation of medication dosage to self-measured glucose levels.

Enhancing adherence

On the theme of adherence-enhancing interventions there exist two systematic reviews. One (Haynes 1997) summarises the results of randomised controlled trials of interventions to help patients follow prescriptions for medication, focusing on those trials that measured both adherence and intervention outcomes. The authors' conclusion is that although adherence and treatment outcomes can be improved by certain - usually complex - interventions, full benefits of medication cannot be realised at currently achievable levels of adherence. No study on diabetes was included. The second systematic review (Roter 1998) assesses the effectiveness of interventions, educational, behavioural and affective categories, to improve patient compliance with medical regimens and concludes that no simple strategy or programmatic focus showed any clear advantage with another. Comprehensive interventions combining different of the studied components were more effective than single-focus interventions. There is also a Cochrane protocol on adherence to medication for controlling blood pressure (Schroeder 2002). With respect to diabetes, two Cochrane Review protocols plan the assessment of the effect of exercise, psychological and lifestyle interventions on the development of future diabetic complications (Boulé 2001; Ismail 2001). A recent review (Renders 2001) concludes that multifaceted professional interventions can enhance the performance of health professionals in managing patients with diabetes. Organisational interventions that improve regular prompted recall and review of patients can also improve diabetes management. The addition of patient-oriented education, can lead to improved patient health outcomes.

Abundant research has pointed at low patient adherence with treatment and life-style recommendations especially in the case of chronic diseases (Vermeire 2001). The management of diabetes is a complex, lifelong process requiring a great deal of effort on the part of the patient. The patient, more than any health care provider, is the key to successful management. Poor management can result in a number of serious complications. Therefore, non-adherence with therapeutic regimens among diabetes patients has been a continuing problem for health care providers (Nagasawa 1990; Vermeire 2001).

Treatment goals

The screening for diabetes, the strict treatment, the follow-up, the self-care and the self-management, and also the efforts to enhance adherence to treatment are to be considered equally important interventions, with the aim of preventing micro- and macro-vascular complications and hence to improve the diabetes patients' quality of life.

Why it is important to do this review

There are no satisfactory data in the literature on the effects of adherence-enhancing interventions on diabetes-related morbidity and mortality, and on the obstacles and constraints patients experience. It has not been assessed, either, what the most effective strategies have in common. Therefore, we attempted to summarise all this information according to strict quality criteria.

OBJECTIVES

To assess the effects of interventions for improving adherence to treatment recommendations in people with type 2 diabetes mellitus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled and controlled trials, before-after and epidemiological studies assessing changes in adherence to treatment recommendations were included.

Types of participants

Inclusion criteria

Studies were included in the review if the participants had type 2 diabetes. This type was formerly called non-insulin-dependent or adult-onset diabetes mellitus. To be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years the diagnosis should have been established using the standard criteria at the time of the beginning of the trial (ADA 1999; Foster 1994; IDF1999; NDDG 1979; Wallach 2000; WHO 1980; WHO 1985; WHO 1998).

Studies in primary care (services of primary health care), outpatient settings (outpatient clinics), community settings (public health services) and hospital settings were included.

Exclusion criteria

We excluded studies investigating:

- type 1 diabetes patients (unless results were reported separately to those for the patients of interest);
- patients that were hospitalised at the beginning of the study (unless results were reported separately to those for the patients of interest);
- interventions to improve exercise or diet .

Types of interventions

(1) Interventions that were aimed at improving the adherence to treatment recommendations were included.
(2) Interventions that were aimed at patients as well as at health care providers.

We considered studies assessing interventions such as:

- education (for example, information, feedback);
- incentives;
- use of electronic devices, decision support systems;
- use of facilitators;
- facilitating of self-recording or self-management;
- scheduling appointments;
- health-care organisation, specific diabetes services;
- health-care provider-patient relationship.

Interventions were compared with each other or with no intervention.
Trials were only included if the intervention was given for a minimum of three months or if the follow-up period after the intervention was a minimum of three months.

Types of outcome measures

Primary outcomes

- health outcomes: diabetes related morbidity (hypoglycaemia and cardiovascular, neurologic, ophthalmologic and nephrologic complications), total and diabetes related mortality (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycaemia or sudden death), hospitalisation rate or readmission rates to hospital, and referral to specialised diabetes care providers (for example physicians, podologists, dieticians);
- direct indicators: blood glucose level, urinary glucose level, glycated haemoglobin concentration, levels of a prescribed drug in the blood, weight, blood lipids (cholesterol, triglycerides), serum creatinine, blood pressure and smoking habits (if the intervention was also aimed at smoking cessation);
- indirect indicators: pill counts, refill records.

Secondary outcomes

We also considered additional parameters:

- subjective report: self-reported or self-monitored adherence, well-being or perceived health quality or patient satisfaction or functional status measured using validated instruments;
- utilisation: appointment making and keeping, use of preventive services1;
- quality of life, well being, perceived health quality (ideally, measured using validated instruments);
- patient satisfaction (ideally, measured using validated instruments);
- functional status defined as the ability to perform daily life activities (for example, walking, preparing meals, communicating with others,...) (ideally, measured using validated instruments);
- obstacles to adherence (for example, dosing, packaging, the treatment's complexity, the understanding of given instructions, issues related to the health care system)
- costs;
- adverse effects of the intervention.

Timing of outcome measurement

Outcomes were assessed in the short (3-6 months), medium (7-12 months) or long term (more than 12 months).

Search methods for identification of studies

Electronic searches

Studies were obtained from searches of multiple electronic bibliographic databases supplemented with hand searches of references and consultation with experts.

We planned to contact companies, but we consulted a number of companies' web sites and bibliographies of company-based studies. Due to the absence of references of studies assessing adherence enhancement companies were not contacted.

The following databases were searched from the beginning of the database to January 2002:

- *The Cochrane Library* (issue 1, 2002) including the Cochrane Controlled Trials Register (CENTRAL) and the Database of reviews of effectiveness (DARE) and the NHS Health Economics Database
- the Metabolic and Endocrine Disorders Group Specialised Register
- MEDLINE
- EMBASE
- PsycInfo
- Eric
- Dissertation and Sociological Abstracts
- Cinahl
- The meta Register of Controlled Trials (http://www.controlled-trials.com)
- Sum Search (http://sumsearch.uthscsa.edu/searchform4.htm) and
- Google search engines (http://www.google.com) on the Internet

Search strategies were adapted from the Cochrane Handbook, the Collaborative Metabolic and Endocrine Disorders Review Group, the Dutch Cochrane Centre and earlier personal search strategies. The following MEDLINE search strategy will be adapted for use with the other databases.

For details of the search strategies see Appendix 1.

Searching other resources

We tried to identify unpublished studies by contacting companies that produce aids for improving adherence (such as electronic devices) and experts who may have known about additional trials.

Studies published in any language were included.

Handsearching

In addition to searching electronic databases, bibliographic searches were performed.

Data collection and analysis

Selection of studies

To determine the studies to be assessed, two teams of independent researchers (EV and JW, PVR and YB) reviewed the titles, abstract sections and keywords of every record retrieved using a score list. The study was included if the information given suggested that the study:

- included patients with type 2 diabetes mellitus;
- assessed adherence to medical treatment, not to exercise nor to diet;
- measured an outcome of an intervention enhancing adherence, and
- used a design as described in the inclusion criteria for study design.

If there was any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent or not clear enough to draw conclusions, the full article was retrieved for clarification. Studies were eliminated if both reviewers agreed that the study did not meet the criteria for considering studies for the review. Inter-rater agreement was calculated using Cohen's kappa (Fleiss 1981) (kappa >0.7 (good agreement), between >0.5 and <0.7 (moderate agreement) and <0.5 (bad agreement)). Differences in opinion were resolved by discussion with a third party (PVR).

Data extraction and management

Three teams of two reviewers (EV and JW, PVR and YB, HH and AL) independently extracted data (the quality criteria, participant details, intervention details, outcome measures, baseline and post-intervention results, and main conclusions), using structured forms for clinical trials and for observational studies. If there was missing information, it was decided that the authors of the article were not contacted. Differences in data extraction at item level were resolved by discussion and if consensus could not be reached, a referee (PVR) took a final decision.

Assessment of risk of bias in included studies

The risk of bias of included studies was assessed independently by three teams of two reviewers (EV and JW, PVR and YB, HH and AL).

To keep up with this process of including and excluding studies a minute description was kept in a log-book. This resulted in a tree structure representation of this process (Moher 1999).

Observational studies are more prone to bias and confounding than experimental trials. Therefore, the methodological evaluation of observational research is not clear cut (Friedenreich 1994; Laupacis 1994; Levine 1994; Stoup 2000).

A set of criteria has been defined for case-control and cohort study designs (Borhouts 1998; Harris 2001; Offringa 2000). Based on these criteria a 3-category rating of 'good,' 'fair,' and 'poor' was applied. In general, a good study is one that meets all criteria well. A fair study is one that does not meet (or it is not clear that it meets) at least one criterion but that has no important limitation that could invalidate its results. A poor study has important limitations. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made.

Cohort and patient-control studies :

(1) were the groups to be compared clearly defined (setting, time, definition of exposition, definition of outcome or adverse effect, criteria for the selection in the cohorts or for the selection for patients and controls)? Good O Fair O Poor O
(2) was selection bias excluded? (case control study) (controls should be a reflection of the source population) Good O Fair O Poor O
(3) were all new cases included? (case control study) Good O Fair O Poor O
(4) were exposure and outcomes equally and independently measured in both groups (information bias)? (case control study) Good O Fair O Poor O
(5) loss-to-follow-up? Good O Fair O Poor O
(6) duration of follow-up? Good O Fair O Poor O
(7) had the analysis corrected for confounders? Good O Fair O Poor O
(8) was there a dose-response relation? Good O Fair O Poor O

Assessment of heterogeneity

We dealt with clinical and methodological heterogeneity to answer the question whether the combination of the different studies was meaningful.

Statistical heterogeneity was estimated by the visual appraisal of the forest plots. Heterogeneity was also tested by using the Z score and the Chi square statistic with significance set at $P < 0.1$. Statistical homogeneity was assessed using the I^2 test where I^2 values over 50% indicate moderate to high heterogeneity (Higgins 2003). If there was significant heterogeneity we had to decide whether the combination of the data was appropriate. If heterogeneity was important, more emphasis should be placed on the results of a random effects model, although use of this model does not overcome the problem of heterogeneity. Another way to handle this issue was to explore possible sources of heterogeneity by subgroup and sensitivity analyses or by employing meta-regression.

Assessment of reporting biases

If there was a reasonable number of studies, a funnel plot would have been drawn to examine the possibility of small study bias. A funnel plot is a graphical display of sample size plotted against effect size. A gap on one side of the wide part of the funnel indicates that some studies have not been published or located or that another type of small study bias has arisen (Egger 1997).

Because the name 'funnel plot' is based on the fact that the precision in the estimation of the underlying treatment effect will increase as the sample size of component studies increases, effect estimates from small studies will therefore scatter more widely at

the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, the plot will resemble a symmetrical inverted funnel (Sterne 2001).

Data synthesis

We undertook a descriptive review of all studies. Data would have been summarised statistically if they were available, of sufficient quality and sufficiently similar. We only would have pooled the effect size of trials with comparable interventions. If not, qualitative synthesis was performed.

We expected both event (dichotomous) data and continuous data. Dichotomous data would have been be expressed as odds ratios (OR). The relative risk (RR) would have been used as an alternative to the OR as interpretation is easier, especially if the outcome is a negative event. Continuous data would have been expressed as weighed mean differences (WMD) and an overall WMD would have been calculated if appropriate.

Subgroup analysis and investigation of heterogeneity

If there was a significant effect for one of the main outcome measures, we aimed to perform subgroup analyses to determine whether there were any systematic differences between groups of patients.
The following subgroup analyses would have been considered:

- age groups (below 60, over 60);
- gender;
- duration of diabetes (below or over five years);
- presence of complications;
- different comparison interventions;
- type of treatment: oral hypoglycaemic agents, insulin, combination of treatments;
- different settings (primary care, outpatient or community settings);
- duration of intervention (short, medium, long term).

Sensitivity analysis

Once the data were analysed, we intended to consider how sensitive the results are to the way the analysis was done. We would have performed sensitivity analyses in order to explore the influence of the following factors on effect size :

- repeating the analyses excluding unpublished studies (if there were any);
- repeating the analyses excluding particular studies on for example combined interventions;
- repeating the analyses excluding studies of the lowest quality (which would have been done already if there was a heterogeneity problem);
- repeating the analyses excluding very long or large studies to establish how much they dominate the results;
- repeating the analyses excluding studies using the following filters: diagnostic criteria, language of publication, source of funding, country, etc.;
- repeating the analysis for single blinded studies.

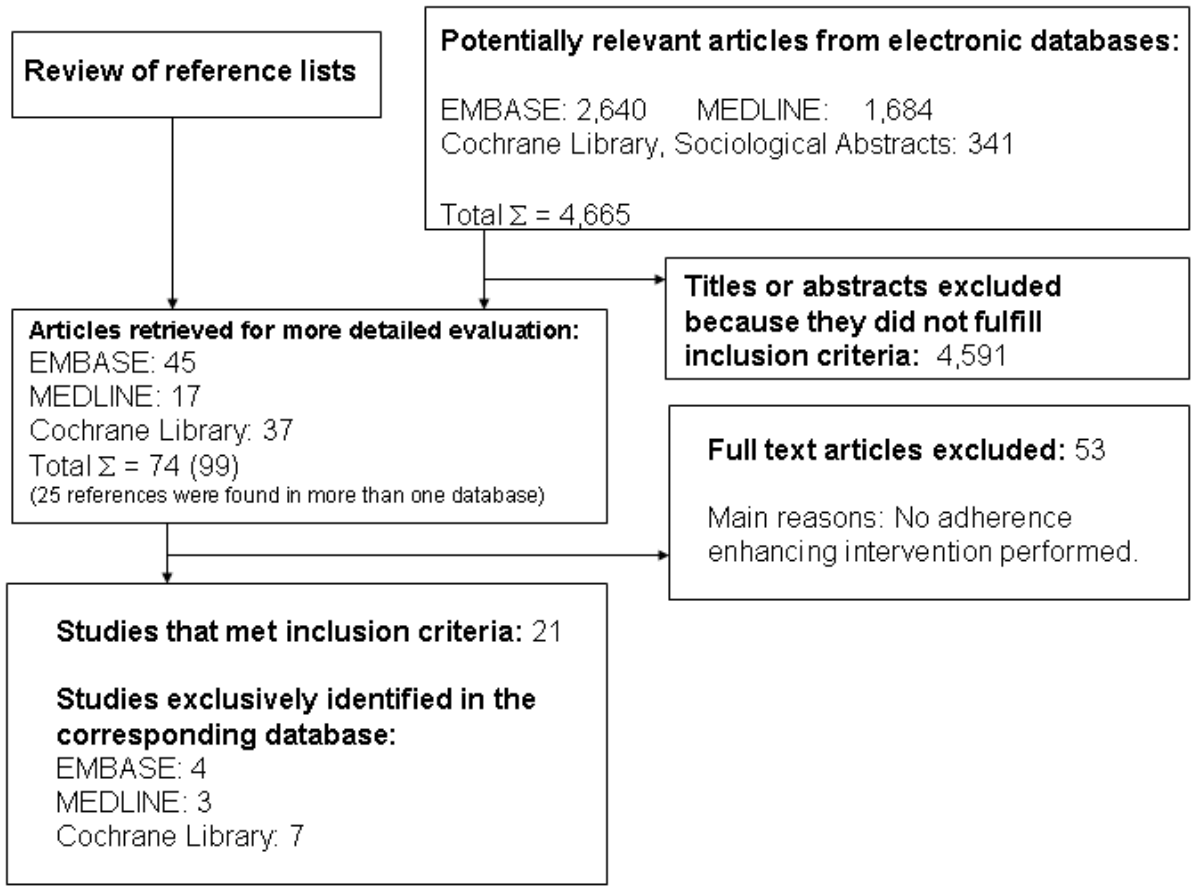
The robustness of the results would have also been tested by repeating the analyses using different measures of effect size (risk difference, odds ratio, etc.) and different statistic models (fixed and random effects model).

RESULTS

Description of studies

The search resulted in 4,665 abstracts. EMBASE contributed 2,640 articles, MEDLINE 1,684, and 341 other studies were added by searches in the Cochrane Central Register of Controlled Trials (CENTRAL), the National Library of Medicine Gateway and Sociological Abstracts (Figure 1). Internet search engines identified hundreds of hits that were informative on the subject, but not useful for the purpose of this review. On initial abstract review, the first apparent reason for exclusion was not meeting the most important inclusion criterion: only studies that assessed interventions aimed at improving the adherence to medical treatment recommendations were accepted. In a large number of studies the precise aim of the study appeared not to be explained clearly at all by the authors. Moreover, in a majority of articles, although adherence was mentioned to be the topic of interest, diabetes care in general or self-care in particular were the core issues of the research reported on. This forced reviewers to careful consideration and led consequently to interrater agreements that improved, and were more consistent, as the selection process went on. Indeed, in many studies interventions aimed at influencing some aspects of diabetes care were, mistakenly and even misleadingly, called enhancing adherence concomitantly.

Figure 1. Study flow diagram



One team of reviewers (PVR and YB) assessed MEDLINE searches and then other team (EV and JW) assessed EMBASE and the other search results. For the purpose of the inclusion, quality assessment and data-extraction of studies an electronic grid was used. It was adapted from a grid originally designed by the Cochrane Metabolic Diseases and Endocrine Disorders Collaborative Review Group.

The interobserver agreement of the first team (PVR and YB) expressed as a kappa was 0.54 (95% CI 0.37 to 0.70), that of the second team (EV and JW) 0.83 (95% CI: 0.76 to 0.89). We identified 74 studies from which in a final round with the full text at hand 52 were excluded, and another one at the time of the analysis. The main reason for their exclusion was that, though authors mentioned in the abstract that the study was about adherence to medical treatment recommendations in type 2 diabetes, no adherence enhancing intervention was performed nor were changes in adherence to treatment recommendation measured properly.

Of the 21 included articles 13 were found in EMBASE, 12 in *The Cochrane Library* and eight in MEDLINE. Four studies were retrieved in EMBASE alone, seven only in *The Cochrane Library* and three uniquely in MEDLINE. Two articles were found in EMBASE, as well as in MEDLINE and in *The Cochrane Library*.

The included studies were: 14 randomised controlled trials (RCTs) (Canga 2000; Hopper 1984; Jaber 1996; Krier 1999; Matsuyama 1993; Mease 2000; Piette 2001; Pullar 1988; Rachmani 2002; Rosenkranz 1996; Simmons 2000; Skaer 1993; Smith 1986; White 1986) including one cross-over study (Diehl 1985), one controlled trial (CT) (Davidson 2000), four controlled before and after studies (CBAs) (Bradshaw 1999; Clarke 2002; Coast-Senior 1998; Jiang 1999) and finally one epidemiological study (Paes 1997).

The studies in this review encompassed a wide range of interventions including nurse interventions, home aids, diabetes education programmes, pharmacy based interventions, interventions comparing the effect of different dosing and frequency of medication intake.
The 21 studies contain data on 4,135 patients.

Only one study evaluating economic aspects of adherence enhancement was identified (Skaer 1993).

Risk of bias in included studies

The methodological quality of each study is described in Characteristics of included studies and in the results section.

Overall judgement of methodological quality

From the 21 included studies three were considered of good, 13 of medium and five of poor methodological quality.

Groups equally provided with care

Groups were equally provided with care in 11 studies (Canga 2000; Davidson 2000; Diehl 1985; Hopper 1984; Krier 1999; Matsuyama 1993; Mease 2000; Rachmani 2002; Rosenkranz 1996; Skaer 1993; White 1986), in one study they were not (Jaber 1996) and data were missing in five studies (Jiang 1999; Piette 2001; Pullar 1988; Simmons 2000; Smith 1986).

Description of losses to follow-up and intention-to-treat analysis

Six studies did not describe losses to follow-up (Bradshaw 1999; Hopper 1984; Jiang 1999; Paes 1997; Rachmani 2002; Skaer 1993), fifteen adequately described losses (Canga 2000; Clarke 2002; Coast-Senior 1998; Davidson 2000; Diehl 1985; Jaber 1996; Krier 1999; Matsuyama 1993; Mease 2000; Piette 2001; Pullar 1988; Rosenkranz 1996; Simmons 2000; Smith 1986; White 1986) and in eight studies it was certain that the authors performed an intention-to-treat analysis (Canga 2000; Davidson 2000; Mease 2000; Piette 2001; Rachmani 2002; Simmons 2000; Skaer 1993; White 1986).

Adequacy of length of follow up

All included study had a follow-up period of at least three months. At the time of performing the analysis one study was excluded because of a follow-up period of only four weeks (Tu 1993).

It is striking that not one author mentioned any data on the calculation of the statistical power of their study.

Allocation

In five randomised controlled trials an adequate randomisation procedure and concealment of allocation could be ascertained (Canga 2000; Diehl 1985; Matsuyama 1993; Piette 2001; Simmons 2000), in six an adequate randomisation but not concealment of allocation could be ascertained (Hopper 1984; Jaber 1996; Krier 1999; Mease 2000; Rachmani 2002; Smith 1986), and in four studies data were missing on both procedures in order to be able to judge properly (Pullar 1988; Rosenkranz 1996; Skaer 1993; White 1986).

Similarity at the start at baseline

At the start of the study groups were similar in 15 trials (Canga 2000; Coast-Senior 1998; Davidson 2000; Diehl 1985; Hopper 1984; Jaber 1996; Krier 1999; Matsuyama 1993; Mease 2000; Piette 2001; Rachmani 2002; Simmons 2000; Skaer 1993; Smith 1986 ; White 1986) and in three articles data were missing (Jiang 1999; Pullar 1988; Rosenkranz 1996).

Blinding

In three studies there was adequate blinding of patients, administrators and outcome assessors (Canga 2000; Piette 2001; Simmons 2000), in two studies there was adequate blinding of patients, but not of administrators and outcome assessors (Krier 1999; Matsuyama 1993), in one study there was adequate blinding of patients, but unclear blinding of administrators or outcome assessors (Diehl 1985), in 11 studies data were missing on any blinding (Clarke 2002; Coast-Senior 1998; Davidson 2000; Hopper 1984; Jaber 1996; Jiang 1999; Mease 2000; Pullar 1988; Rachmani 2002; Smith 1986; White 1986) and one study did definitely not apply any form of blinding (Rosenkranz 1996).

Effects of interventions

We did not find any data on quality of life, mortality or morbidity in the included studies, nor did we retrieve any information on cost-benefits of adherence enhancing interventions.

According to the nature of the interventions studies were grouped in a logical way.

'Nurse interventions' (Clarke 2002; Mease 2000; Piette 2001) compared nurse-led interventions, mostly a telephone follow-up, with usual care. In these studies a variety of outcomes were evaluated, but unfortunately they were heterogenous in the different studies: HbA1c, weight, diabetes related symptoms, appointment keeping, changes in medication taking, changes in uses of preventive services, and self-care behaviour.

'Home aides' (Hopper 1984; Smith 1986) are mailed educational materials, appointment reminders or home health aides visits versus usual care, evaluating appointment keeping, prescription refill, screening percentage, eye clinic attendance and negative utilisation of services (emergency room visit, missed scheduled visits).

'Diabetes education programmes' (Bradshaw 1999; Jiang 1999; Krier 1999; White 1986) assessed the effect of a variety of education programmes on HbA1c, different metabolic parameters, blood pressure and self-reported compliance.

'Pharmacy based interventions' (Coast-Senior 1998; Davidson 2000; Jaber 1996; Matsuyama 1993; Skaer 1993) assessed the effectivity of pharmacist-led interventions (pill count, MEMS, comprehensive care, treatment adjustments, prescription refill reminders) on self-reported adherence, medication prescription refill, and some metabolic parameters.

'Dosing and frequency' (Paes 1997; Pullar 1988; Simmons 2000) interventions assessed the effect of calendar blister packs and once up to three times daily medication intake on compliance.

Besides these created categories there remain four *solitary comparisons*: standard consultation versus a patient participation programme (Rachmani 2002), oral chlorpropamide intake versus insulin injections (Diehl 1985), fundus photography shown and explained versus not shown nor explained (Rosenkranz 1996), and finally a nurse-led education and counseling intervention on smoking cessation (Canga 2000).

We pooled the studies assessing educational interventions: those facilitating adherence (Krier 1999; Piette 2001; Rachmani 2002; Simmons 2000; White 1986) and those offering diabetes education (Coast-Senior 1998; Jiang 1999) versus usual care or a control. In all these studies HbA1c was a common outcome measure.

The results of the 21 included studies are reported narratively, though some of the comparisons fit for the calculation of pooled weighted mean differences. Because within each of these trials methods, patients and many other characteristics are unlikely to be identical, as would be implied by the use of a fixed effect meta-analysis model, a random effects model was used. The educational

intervention trials were pooled. The studies offering diabetes education with outcome measure HbA1c could not be used in a meta-analysis because these studies were controlled before and after trials.

Nurse led interventions

The comparison of the effectiveness of education classes plus weekly nurse telemedicine 'home visit' versus usual care (Mease 2000) , over a period of three months, shows a statistically significant reduction in mean HbA1c level of 0.4%. The mean weight reduction is limited to a non significant 4%. Furthermore there were no significant changes on a Diabetes Quality of Life scale nor on the Medical Outcome Health Survey SF-36 scale. Some metabolic parameters such as microalbuminuria, serum creatinine and serum lipids did not improve during the study period. Physicians and case managers considered telemedicine to have a high benefit, but technological problems were a major obstacle.

A 12 months telephone nurse-led follow-up intervention (Piette 2001) in which a nurse called patients weekly to talk about self-care, medication adherence and symptoms, showed a small but statistically significant (P = 0.04) lowering of HbA1c. Moreover patients in the intervention group reported fewer (-10%) diabetes related symptoms, while these increased with the same proportion in the control group.

Another 12 months telephone calls programme (Clarke 2002) focused on improving participants' understanding of their disease and the crucial importance of adhering to standards of care while providing support in helping patients to change their behaviour and lifestyle. Authors assessed subjective reports of adherence and measured utilisation of medical services. There were no differences in the mean change score of medicine taking, of taking recommended medical tests nor in the use of preventive health services. Patients in the intervention group had more frequently testing of HbA1c, low density lipoproteins, microalbuminuria and diabetic retinopathy.

Home aids interventions

Appointment keeping and prescription refills were the outcome measures of a 12 months' study of the effectiveness of mailed packets (physician phone numbers, visiting hours, list of early warning signs), a booklet on management of diabetes, appointment reminders, accompanied by an intense follow-up of visit failures versus usual care (Smith 1986). After one year the intervention group averaged 12% more total contacts than the control group (5.8 versus 5.2, P = 0.01), due largely to an increase in kept scheduled visits (4.1 versus 3.6, P = 0.006). Visit failures were mainly reduced in high-risk patients and those patients at higher risk of hospitalisation. The effect of the intervention did not diminish during the year of the study.

The impact of home health aides visits on diabetic control and health care utilisation was assessed on fasting blood glucose, eye clinic attendance and negative utilisation of medical services (Hopper 1984). Fasting blood glucose declined when compared to control group (10.1 mg/dl versus an increase of 5.1 mg/ dl). Missed clinic appointments and attendance of emergency room decreased slightly in the intervention group, and eye clinic attendance increased significantly ((1.3 versus 0.7, representing a change of 0.4 (95%CI 0.1 to 0.7) versus -0.02 (95%CI -0.3 to 0.3)).

Diabetes education interventions

A nine months study comparing quarterly visits of a diabetes educator versus usual care, assessed changes in HbA1c, weight and self-reported medical compliance on a 4-point Lickert scale (Krier 1999). Neither group showed any statistical significant change in their HbA1c. Weight increased in both intervention and control groups. There was a small increase in self-reported medical compliance in both intervention and control groups.

Another RCT compared group management with an advice-educational technique on its effect on HbA1c (White 1986). There was a 10% decline in HbA1c levels (P < 0.05) in the first three months of the study in both groups, However, little change occurred during the final three months of the study.

The effect of a five-section education program during four months was compared to a basic course, and evaluated by measurement of fasting blood glucose, HbA1c, serum cholesterol, triglycerides, blood pressure and body weight (Jiang 1999). In both experimental and control groups the decline in HbA1c levels was statistically significant (9.4% to 8.7%, versus 9.3% to 9.0%). In the experimental group the decline in systolic blood pressure and body weight was statistically significant.

The effect of three structured educational programs (traditional, video, educator) assessed HbA1c, weight and mean change in levels of knowledge (Bradshaw 1999). The authors indicate that there was no effect on the levels of HbA1c or weight, but data are missing. There was a significant increase in percentage of correct answers on knowledge questions on diabetes in the group with educator.

Patient participation consultation

A four years study compared the effect of standard consultations with a patient participating programme in which patients shared therapeutic responsibilities (Rachmani 2002). HbA1c, blood pressure, LDL and the number of cardiovascular events was evaluated in both groups. All outcome measures declined in a statistically significant way in the intervention and control groups.

Pharmacy based interventions

During a four months intervention comparing adherence data from a medication event monitoring system (MEMS) with pill counts in assisting pharmacists in making recommendations regarding diabetes therapy (Matsuyama 1993) did not show any significant change in metabolic control. There were no significant changes in non-adherence in both groups. In the MEMS group, 47% of the recommendations regarding diabetes therapy made by pharmacists were related to patient education compared to 12% in the control group.

In a four month period, a comprehensive pharmacist care model was compared to usual care (Jaber 1996). Patients in the intervention group were offered diabetes education, medication counseling, and evaluation plus adjustment of their hypoglycaemic regimen. Significant improvement of HbA1c levels was obtained (P = 0.003) in the intervention group. No significant changes in blood pressure control, lipid profile, renal function parameters, weight, or quality of life measures was noted between groups.

The effectiveness of mailed prescription-refill reminders, specialised packaging, or a combination was assessed versus usual care in a one year study on the medication possession

ratio (number of days' supply of medication obtained throughout 360 days of the trial) (Skaer 1993). Patients receiving mailed prescription-refill reminders, unit-of-use packaging, or a combination of both interventions achieved a significant (P < 0.05) increase in the medication possession rate for sulphonylurea therapy relative to controls. No significant difference was discerned between groups receiving reminders or special packaging. Patients receiving both interventions experienced a significant decrease in the use of physician, laboratory and hospital services reaching 68 US dollars decrease per capita compared to the 3-month time frame prior to the study. In the experimental group however, much more hypoglycaemic episodes occurred than in the control group (17 versus 2). The authors indicate that the systolic blood pressure improved, but the article does not allow to discern whether within or between group data are presented. HbA1c declined within and between groups. There was a higher decline in persons with a higher start level. There were no changes in body weight, serum lipids and renal function between or within groups. There were no data on self-reported adherence to medication. There were also no changes in scores on validated Health Status and quality of life questionnaires.

The effect of a one year pharmacist treatment adjustments versus standard physician led care on HbA1c, appointment keeping, eye examination and refusal to make recommended medication adjustments was studied (Davidson 2000). The HbA1c levels fell significantly (-0.8% versus -0.05%) in the intervention group more than in the control group (P = 0.03). In this study compared groups were not clearly defined and there are no data on losses to follow-up.

The effectiveness of pharmacists initiating insulin treatment on HbA1c was evaluated after one year (Coast-Senior 1998). HbA1c levels decreased by 22% (P < 0.05). On the contrary symptomatic hypoglycaemic episodes occurred in 35% of patients.

Oral antidiabetic drugs versus insulin

In a two times 24 weeks cross-over study compliance to the oral intake of chlorpropamide was compared to insulin injections (Diehl 1985). Adherence to treatment was evaluated as the percentage of expected tablets or insulin used. There were no differences in adherence with the two medications in terms of percent of prescription used, proportion taking at least 80% of prescribed medication, self-report of medication or diet compliance, or protocol dropout rates. However, treatment satisfaction was higher with chlorpropamide.

Dosing and frequency

The adherence to oral medication according to an intake of once, twice or three times a day was evaluated by tablet count and the detection of the level/dose phenobarbital ratio - as a chemical marker of medication intake (Pullar 1988). Inadequate compliance was defined as either interview evidence of having missed some study tablets, a value for compliance by tablet count less than 85%, or a phenobarbital level dose ratio less than 85%. Mean compliance for once daily dosing was significantly higher than for twice a day (P < 0.05) or three times a day (P < 0.05).

HbA1c and blood pressure were evaluated after four and eight months in patients receiving calendar blister pack compared to the usual delivery of tablets (Simmons 2000). HbA1c was reduced by 0.95 ±0.22% in the calendar group and 0.15 ±0.25% in the control group (P = 0.026). Diastolic blood pressure decreased significantly, in contrast with systolic blood pressure that remained unchanged.

In an observational study (Paes 1997) adherence with dosing and medication prescription refill was measured with MEMS, pill counts and by analysis of pharmacy records. This study observed that compliance is influenced by the frequency of doses. The compliance, the percentage of doses taken measured by MEMS during the six months observation period in this study, was 98.7% (SD 18.6) in the case of a once daily dose and 65.8% (SD 30.1) in the case of a dose of three times daily. Refill compliance with prescribed regimen was 79.1% (SD 18.8) in the once daily regimen and 38.1% (SD 35.8) in the three times a day regimen.

Fundus photography

To investigate whether instantaneous Polaroid fundus photography during a patient consultation would effect patient's future screening behaviour, three groups of patients were evaluated: those to whom the picture was not shown, versus those to whom the picture was shown, explained and handed out, versus to whom the picture was shown, explained but not handed out (Rosenkranz 1996). The outcome measure was future appointment keeping with the ophthalmologist and was 51%, 80% and 68% respectively in described patient groups.

Smoking cessation

To assess the effectiveness of a six months nurse-led education and counseling programme on smoking cessation, self-reported and verified smoking cessation as well as the change in mean cigarettes per day was evaluated versus usual care (Canga 2000). Smoking cessation incidence was 17% in the intervention group compared with 2.3% in the usual care group, which was a difference of 14.7% (95%CI 8.2 to 21.3%). The mean number of cigarettes per day decreased from 20 to 15.5 (-4.6 cig/d; 95%CI -3.3 to -6) at six months follow-up for the experimental group versus from 19.7 to 18.1 for the control group (-1.6 cig/d; 95% CI -0.4 to -2.8) (P < 0.01). Another study assessed the effect of three structured education programmes (traditional, video and educator) on patient reported smoking cessation (Bradshaw 1999). Of the smoking participants 41% reported they had ceased over the period of the study.

DISCUSSION

Summary of main results

The aim of this review was to identify effective interventions or strategies to enhance adherence to treatment recommendations in people with type 2 diabetes in primary care, outpatient settings, community and hospital settings.

A large number of studies was identified, but only 21 articles were included in the review. This is mainly due to the fact that though many authors stated that their study was about compliance or adherence the core issue was self-care or some aspect of diabetes management. Many authors do not feel the need to define adherence, nor do they discuss in which way and to what extent the outcome measures used really reflect adherence! Only a few articles measured adherence directly or indirectly using questionnaires. For these reasons we had to adapt one of the inclusion criteria from 'assessment of an intervention to enhance adherence' in 'assessment of an intervention aimed at improving adherence'. Many studies seem to report on 'black box" research:

doing an intervention and measuring HbA1c at the end of the study period. In many studies it remains unclear what really happened in those participants, what made metabolic parameters change or what made them remain unchanged? Besides, what way does adherence play a role if an outcome changes?
Therefore it was not an easy task for the reviewers to decide on inclusion or exclusion. Moreover, this process was very time consuming.

The studies included in the review are heterogeneous in terms of interventions, participants, settings, countries and outcomes. The majority of studies used a set of outcome measures which do not lead to consistent and homogeneous results. Even interventions aimed at improving diabetes care in general do not result in homogeneous results for different aspects. It is clear that a rather 'simple' intervention as a diabetes education programme is not able do have consistent and homogeneous effects in a complex disease, as is the case for diabetes mellitus. It is indeed imaginable to conclude that an effective adherence enhancing intervention does not lead to satisfactory declining HbA1c values. Diabetes management is indeed much more than taking medication alone. Moreover, an effective intervention may lower some metabolic parameters, without affecting other parameters such as weight, blood pressure or renal function. Indeed, did UKPDS not confront researchers first with the paradox that tight glycaemic control induced an increase in HbA1c values and second with the conclusion that tight blood pressure control was more effective than tight glycaemic control in hypertensive diabetic persons in reducing diabetes related morbidity and mortality? Therefore, there is a need for better research discerning between adherence enhancing strategies and their effect on diabetes related outcomes.

The methodological quality was often limited. Besides the criteria for quality that are presented in the table with the characteristics of included studies, more remarks can be made. The most important question remains that of the validity of the studies because of low numbers of participants, lack of power calculations, poor or absent definition of adherence and the assumption that metabolic parameters such as HbA1c adequately reflect adherence. Moreover, regarding the educational interventions concerned, these were so poorly described that it was not possible to discern differences or similarities between programmes.
In a majority of articles the quality of the reporting in the written articles was incomplete and inaccurate such as missing data, incomplete figures or tables and the absence of confidence intervals or standard deviations.

Therefore, it is difficult to draw general conclusions from this review. In general most results float around the zero line, which may be interpreted by saying that there are no effective interventions or, by saying that the quality of the research was so poor that it was not able to reveal any significant effect. HbA1c declined slightly in most of the studies, furthermore positive effects could be noted on appointment keeping, eye clinic attendance, improved knowledge of diabetes, and prescription refill adherence. Once daily dosing appeared to be effective in increasing oral medication intake.

Our conclusions on the effectiveness of educational interventions on metabolic control are concordant with those of a UK Health Technology Assessment systematic review (Loveman 2003). These authors conclude that education as part of intensification of treatment produces improvement in diabetic control in type 1 diabetes. In type 2 diabetes they find mixed results which means that no clear classification is possible as to what features of education may be beneficial. A diversity of educational programmes did not yield consistent results on measures of metabolic control, with studies of lower quality producing significant effects. Economic evaluations comparing education with usual care or other educational interventions in type 2 diabetes mellitus were not identified. A recent review on dietary advice was not able to find any effectivity, though the adoption of exercise appeared to improve glycated haemoglobin at six and twelve months (Moore 2004). Psychological interventions showed improvements in long-term glycaemic control but not in weight control or blood glucose concentration. The pooled mean difference in HbA1c was -0.3 (95% CI -0.6 to 0.1) (Ismail 2004).

This review illustrates the necessity that all relevant databases should be consulted. MEDLINE, EMBASE and the Cochrane Controlled Trial Register contributed almost equally to the included studies (Wens 2004).

The majority of the authors drew positive conclusions while presenting statistically significant differences between intervention and control groups. In contrast, it is crucial to notice that those results were probably not very clinically relevant.

Because almost all HbA1c values floated around the zero line we decided not to perform sensitivity analyses in order to explore the influence on a number of factors on the overall effect size.

The problems encountered are not typical for this review. Recently, a systematic review was published on adherence improving to blood pressure lowering medication, in which authors described exactly the same problems and pitfalls. They were not able to draw general conclusions, only but the assumption that reducing the number of daily doses appears to be effective in enhancing adherence in ambulatory care (Schroeder 2004).

Regarding to the fact that there we just a few studies available, the funnel plot was not performed due to the lack of reliability in this case.

The results of this review are concordant with an earlier Cochrane Review that summarised the results of RCTs of interventions to help patients, without any specific medical condition, follow prescriptions for medication, focusing on those trials that measured both adherence and outcomes. No effective interventions were identified.

The conclusions of an earlier narrative review of the compliance/adherence literature (Vermeire 2001) are concordant with those of this systematic review: though every health care professional considers adherence to be an crucial element in health care, though everyone recognises non-adherence as a major health care problem, though every scientist ascertains that diabetes mellitus may be considered a new epidemic in the decades to come, the evidence base on adherence to treatment recommendations in diabetes is almost inexistent.

AUTHORS' CONCLUSIONS

Implications for practice

Current efforts to improve or facilitate adherence of people with type 2 diabetes to treatment recommendations do not show significant effects nor harms. The question whether any

intervention enhances adherence to treatment recommendations in type 2 diabetes effectively, thus still remains unanswered.

Implications for research

In research on the effectiveness of interventions a number of, generally accepted but not generally applied, rules ought to be respected. With regard to adherence research methodological flaws mainly refer to the research question, the definition of and measure instruments for adherence. Quite often the research question is not clearly formulated, neither is adherence defined properly. If adherence is not well defined in the first place, how is it possible then to operationalise enhancement of adherence in the second place?

Besides, the measurement instruments for adherence should be apt to measure adherence. Mostly adherence is assessed indirectly, leaving the reader with the question how valid this research was.

This type of flawed and biased research does not appear to be very conclusive. In addition, different study findings cannot be compared easily. The question whether any intervention enhances adherence to treatment recommendations in type 2 diabetes effectively, thus still remains unanswered.
Adherence should be defined explicitely, the measurement instruments should be as direct as possible, assuring that the established changes really reflect effects of the intervention on adherence itself. Indeed, researchers studying adherence should be careful not to be biased too easily by the results of 'black box' research in which any measured effect is assigned to an intervention that has being taken place before. There may not doubt about the causal relationship between the intervention and the outcome.

Next the encountered variety of educational interventions that has been tested, in the many excluded studies as well, reflects that the choice of components of education programmes is often not based on a theoretical or empirical rationale. Many authors say that education is the cornerstone of diabetes management, they study a programme they designed, leaving everyone in a state of uncertainty about which aspect of the education, hence which combination of components, and which duration are determinants for better adherence. Finally there is a need to know whether interventions have an effect on the short term, a long acting effect, or whether they need to be repeated periodically. In adherence research, evidence based economical evaluations are missing. When effective interventions will be revealed in the future, their impact on human and financial resources merits prime attention.

In recent years attention is being paid to a shift from compliance to concordance and shared-decision making. The quality of the health care provider - patient encounter takes into consideration the patient's health beliefs, medication and treatment recommendations review. In concordance, the treatment regimen is tailored to what is manageable and attainable for this particular person. A robust research evidence based on this topic needs to be built in future research projects.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bradshaw 1999

Methods	- Controlled before and after study - Groups clearly defined - Selection bias can be excluded - Losses to follow-up: not described - Duration of follow-up: clearly defined - No correction for confounders - Overall judgement of quality: medium
Participants	- 230 type 2 diabetes patients - United Kingdom - Urban - Recruitement in primary care services - Traditional (87), Video (86), Educator (57) - Sex: M 52.2 % - Age: mean 66.4, traditional (M: 66.7%), video (M: 46.8%), educator (M: 58.5%) - Smoking: 22.2 %, traditional 28.7 %, video 23.3 %, educator 10.5% - Weight: mean 77.9 kg - HbA1c: mean 7.35, traditional 7.63, video 7.35, educator 6.91
Interventions	To assess the effectiveness of three structured educational programmes (traditional, video and educator) on foot care, management and natural history of diabetes.
Outcomes	Change in levels of knowledge, HbA1c, blood glucose, reported smoking cessation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Canga 2000

Methods	- Randomised controlled trial - Randomisation and concealment of allocation: adequate - Adequate blinding of patients, administrators and outcome assessors - description of losses to follow-up and intention-to-treat analysis - Groups similar at the start of the study - Groups equally provided of care - Overall judgement of quality: good
Participants	- 280 type 2 diabetes patients in outpatient settings in an urban area in Spain - Multicentre study - Sex: intervention (F: 22, M: 125), control (F: 18, M: 115) - Age: intervention (54.4 +- 15), control (55.8 +- 14.9) - Daily cigarettes: intervention (19.9 +- 11.9), control (19.8 +- 11.5) - Years of smoking: intervention (36.4 +- 16), control (38 +- 15.2) - BMI: intervention (27.0 +- 4.7), control (26.2 +- 4.4) - treatment modality: insulin (intervention 47, control 47)

Canga 2000 *(Continued)*

Interventions	Nurse-led education and counseling versus usual care for smoking cessation.
Outcomes	Self-reported and verified smoking cessation. Change in mean cigarettes per day.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	

Clarke 2002

Methods	- Controlled before and after study - Blinding (patients, outcome assessors): no - Losses to follow-up: clear - Duration of follow-up: clear - Overall judgement of quality: poor
Participants	- 748 type 2 diabetes patients - Multicentre study, patients recruited in primary care services - Sex: F: 386, M: 362 - Age: mean 59
Interventions	To evaluate the effect of a Diabetes Healthways management programme. Behaviour and metabolic outcomes of patients enrolled are compared before and after. Nurse call system aimed at formulating health care goals and reinforcing behavioural changes.
Outcomes	Change in medication taking, change in use of preventive services, HbA1c, LDL, diabetic retinopathy (DRE), microalbuminuria
Notes	Of the 2982 patients enrolled , 748 were assessed in the survey. No baseline characteristics are shown for the enrolled population, though the survey sample is claimed to be representative.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Coast-Senior 1998

Methods	- Controlled before and after study - No blinding - Adequate description of losses to follow-up - Groups similar at the start of the study - Overall judgement of quality: medium
Participants	- 23 type 2 diabetes patients - Single centre study in an urban area in the USA - Patients recruited in primary care services - Sex: M: 23

Coast-Senior 1998 *(Continued)*

	- Mean age: 65, SD 9.4 - HbA1c: 11.1%, SD 1.6 - Fasting blood glucose: 219 mg/dL 219, SD 45 mg/dl - Random blood glucose: 236 mg/dl, SD 72 mg/dl - Duration since diagnosis: 8.8 years, SD 4.2 - Treatment modality: diet + oral hypoglycaemic agents + insulin: 23
Interventions	To determine the impact of clinical pharmacists, involved in direct patient care, on the management of patients with type 2 diabetes who require insulin. Patients were referred to clinical pharmacist for management of diabetes: the intervention included an initial interview, initiating insulin treatment and adjusting insulin doses by pharmacists, and follow-up by appointment or phone call.
Outcomes	HbA1c, fasting blood glucose (FBG), random blood glucose
Notes	Participants were veterans with multiple co-morbidities (mean 4, range 2-8) and on multiple medications (mean 5, range 2-10)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	High risk	

Davidson 2000

Methods	- Controlled, not randomised trial - No blinding of patients or administrators, blinding of outcome assessment unclear - Intention-to-treat-analysis - Groups were similar at the start of the study - Groups were equally provided of care - Overall judgement of quality: medium
Participants	- Single centre study in primary care services in the USA - Particpants: 181 type 2 diabetes patients (intervention: 89, control: 92) - Sex: intervention (F: 42, M: 47), control (F: 46, M: 46) - Mean age: intervention (54.8 years), control (51.8 years) - Ethnicity: intervention (Afro-American 14.6%, Caucasian 14.6%, Hispanic 69.7%), control (Afro-American 17.4%, Caucasian 15.2%, Hispanic 64.1%, other 2.2%, undetermined 1.1%) - Hypertension: intervention (67.4%), control (45.6%) - HbA1c: intervention (8.8% (0.2) n=79), control (7.9 % (0.2), n=73) - Retinopathy: intervention (n=29), control (n=14) - Neuropathy: intervention (n=21), control (n=8) - Nephropathy: intervention (n=35), control (n=13) - Diabetic foot: intervention (n=15), control (n=1) - Macrovascular complications (coronary artery disease or cerebrovascular disease): intervention (n=5), control (n=8) - Treatment modality: diet alone (intervention 0, control 8), oral hypoglycaemic agents (intervention: 38, control: 51), insulin: (intervention: 20, control: 19), diet+oral agents+insulin: (intervention: 31, control 14)
Interventions	To evaluate an evidence-based process in a free medical clinic in patients referred to pharmacists using detailed algorithms versus standard physician led care.
Outcomes	Change in HbA1c, refusal to make the recommended medication adjustements, appointment keeping, eye examination.

Davidson 2000 *(Continued)*

Notes	Of the 89 participants in the intervention group 12 had type 1 diabetes, as did 9 persons in the control group. The intervention group has been referred is 'sicker' than the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Diehl 1985

Methods	- Cross-over study - Adequate randomisation - Adequate patient blinding, unclear blinding of administrators, and data missing on blinding of outcome assessors - Adequate description of losses to follow-up - No intention-to-treat analysis - Groups were similar at the start of the study - Groups were equally provided of care - Overall judgement of quality: medium
Participants	- Single centre study in the USA - 77 type 2 diabetes patients recruited in outpatient settings - Participants: intervention (chlorpropamide 40), control (insulin 37) - Sex: intervention (F: 29, M: 11), control (F: 26, M: 11) - Age: intervention (50.6 yrs, SD 9.5), control (51.2 yrs, SD 9.3) - Ethnicity: intervention (95% Mexican-American), control (91.9% Mexican-American) - Glycaemia: intervention (236.3 mg/dl, SD 81.5), control (243.6 mg/dl, SD 73.3) - Treatment modality (prior to study): diet alone: intervention (40), control (37)
Interventions	To compare compliance with chlorpropamide versus insulin among persons newly treated for type 2 diabetes.
Outcomes	Percentage of expected medication taken, estimation of medication taken by patients, dropout rates, description of adherence on a 4 point scale, participants' attitudes and satisfaction.
Notes	

Hopper 1984

Methods	- Randomised controlled trial - Randomisation adequate. - Concealment of allocation: data missing - Blinding of patients and administrators: data missing - Blinding of outcome assessors: data missing - Losses to follow-up: data missing - Intention-to-treat analysis: no - Groups similar at the start of the study - Groups equally provided of care - Overall judgement of quality: poor
Participants	- 227 type 2 diabetes patients - Outpatients in a city in the USA - Participants: intervention (114), control (113) - Sex: intervention (F: 83, M: 31), control (F: 84, M: 29)

Hopper 1984 *(Continued)*

	- Mean age: intervention (59), control (57) - Ethnicity: intervention (Black 90), control (Black 79) - Blood glucose: intervention (226 95%CI 214-238), control (221 95% CI 209-233) - Duration since diagnosis: intervention (11 years), control (12) - Treatment modality: oral hypoglycaemic agents: intervention (19%), control (23%) - Treatment with insulin: intervention (81%), control (77%)
Interventions	Home health aids
Outcomes	Fasting blood glucose, eye clinic attendance, negative utilisation (emergency room visits, missed visits)
Notes	

Jaber 1996

Methods	- Randomised controlled trial - Adequate randomisation - No blinding of patients and administrators, unclear blinding of outcome assessment - Losses-to-follow-up adequately described - No intention-to-treat analysis - Groups were similar at the start of the study - Groups were not equally provided of care - Overall judgement of quality: medium
Participants	- Single centre study in a city in the USA - Outpatients - 39 type 2 diabetes patients (intervention 17, control 22) - Sex: intervention (F: 12, M: 5), control (F: 15, M: 7) - Mean age: intervention (59, SD 12), control (65, SD 12) - Ethnicity: intervention and control groups: 100% African American - Mean weight: intervention (93 kg, SD 22), control (88 kg, SD 19) - BMI: intervention (34, SD 7), control (33, SD 7) - BMI > 27: intervention (13), control (18) - Systolic blood pressure: intervention (140 mmHg, SD 20), control (143, SD 23) - Diastolic blood pressure: intervention (82, SD 10), control (88, SD 9) - Hypertension: intervention (14), control (17) - Lipid abnormalities: intervention (10), control (11) - HbA1c: intervention (11.5%, SD 2.9), control (12.2%, SD 3.5) - Fasting blood glucose: intervention (11.1 mmol/l, SD 4), control (12.7 mmol/l, SD 4.7) - Duration since diagnosis: intervention (6.8 years, SD 6.5), control (6.2 yrs, SD 4.8) - Treatment modality: diet + oral hypoglycaemic agents: intervention (17), control (22) - Exclusion criteria: IDDM, renal dysfunction, history of non-attendance
Interventions	To determine the impact of a comprehensive pharmaceutical care model (pharmacist provided care) versus standard care on treatment outcomes of NIDDM urban African Americans. Specific items of care were: evaluation and adjustment of doses, education regarding diabetes and its complications, training on recognition of hypoglycaemia and hyperglycaemia, instructions on diet and exercise, training in self-monitorig of blood glucose. Treatment was titrated to targets.
Outcomes	Blood glucose control, self-recorded adherence, and self-monitoring blood glucose logs
Notes	Self-monitoring mentioned, but not specified and no data were presented.

Jiang 1999

Methods	- Controlled before and after study - Patient , administrator of treatment, and outcome assessment blinding: data missing. - Descritpion of losses to follow-up are missing - No intention to treat analysis - Similarity of groups at the start of the study: not mentioned - Groups equally provided of care: data missing - Overall judgement of quality: poor
Participants	- Multicenter study in urban areas in Taiwan. - 217 type 2 diabetes patients in an outpatient setting. - Inclusion criteria: aged between 35 and 70 years old, able to read, HbA1c level >/=8.0% and with stable metabolic control. - Sex: intervention (F 61, M 69), control (F 49, M 38) - Age: intervention (52.3 +- 6.7), control (52.9 +- 7.4) - Body Mass Index: intervention (25.2 +- 3.5), contol (25.6 +- 3.2) - Duration of disease since diagnosis: intervention (8.0 years +- 8.0), control 6.7 yrs +- 5.3) - Treatment: Diet and oral hypoglycaemic agents: intervention 121, control 87
Interventions	A 5 section education program was offered to type 2 diabetes patients. Diabetes self-care was assessed before and 4 months after attending a diabetes education programme including basic knowledge, dietary control, blood glucose monitoring, management of hypoglycemia, medication compliance, foot care and exercise. A total of 121 attended four to five sections and were called the intervention group, and the 87 who only received the basic section were called the control group.
Outcomes	Fasting plasma glucose, HbA1c, total cholesterol, triglycerides, systolic and diastolic blood pressure, body weight, and waist-hip ratio.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Krier 1999

Methods	- Randomised Controlled Trial - Randomisation adequate - Patients are blinded, but not the administrator of treatment, and on blinding of outcome assessment data are missing. - Losses to follow-up described. - Intention-to-treat analysis: unclear - Groups were similar at the start of the study. - Groups were equally provided of care. - Overall judgement of quality: medium
Participants	- 39 type 2 diabetes patients living in a city in the United States. - 21 people were allocated to the intervention group and 18 to the control group. - Sex: intervention (F: 9, M: 5), control (F: 10, M: 4). - Age: intervention (54.2 +- SD 5.6), control (56.2 +- SD 9). - Ethnicity: intervention (6 Afro Americans), control (7 Afro Americans). - Smoking: intervention (3), control (3). - Weight: intervention (97.4 kg +- 23.9), control (93.8 +- 19.4). - Locus of control: intervention (4.5 +-1), control (4.0 +- 1.1). - Knowledge test: intervention (11.3 +- 3.8), control (14.2 +- 3.6). - HbA1c: intervention (9.6% +- 1.9), control (10.3% +- 2.3).

Krier 1999 *(Continued)*

	- Treatment modality: oral hypoglycemic agents (intervention 8, control 7), insulin (intervention 5, control 5), combination (intervention 1, control 2).
Interventions	To evaluate the effect of quarterly visits of a diabetes educator versus usual care.
Outcomes	HbA1c, 4-point Lickert scale on compliance with diet and medication.
Notes	

Matsuyama 1993

Methods	- Randomised controlled trial - Adequate randomisation and concealment of allocation - Blinding of patients and adminstrators of treatment - No blinding of outcome assessors. - Losses to follow described - No intention-to-treat analysis - Groups were similar at the start of the study - Groups were equally provided of care - Overall judgement of quality: medium
Participants	- 32 type 2 diabetes outpatients (USA veterans) - Single centre study in an urban area in the USA - Participants: intervention: 15, control: 17 - Sex: intervention (M: 15), control (F: 1, M: 16) - Age: intervention (mean 64 years, SD 7), control (mean 64 yrs, SD 8) - HbA1c: intervention (12.7%, SD 1.9), control (12.1 %, SD 2.6) - Glycaemia: intervention (12.1 mmol/l, SD 1.9; 167.81 mg/dl, SD 35.57), control 11.1 mmol/l, SD 2.9; 147.63 mg/dl, SD 38.57) - Duration since diagnosis: intervention (6.7 years, SD 7.6 yrs), control (8.5 years, SD 8.5 yrs) - Treatment modality: oral hypoglycaemic agents: intervention 15, control 16
Interventions	To compare adherence data from a medication event monitoring system (MEMS) with pill counts in assisting pharmacists in making recommendations regarding diabetes therapy.
Outcomes	MEMS and pill count adherence rates.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	

Mease 2000

Methods	- Randomised controlled trial - Adequate randomisation - Unclear blinding of patients, administrators or outcome assessors - Adequate description of losses to follow-up - Intention-to-treat analysis - Groups were similar at the start of the study and were equally provided of care

Mease 2000 *(Continued)*

	- Overall judgement of quality: medium
Participants	- Single centre study in the USA - 28 Type 2 diabetes patients recruited in primary care services - Inclusion: HbA1c >8.0%
Interventions	To determine whether telemedicine can improve self-care for type 2 diabetes: education classes and weekly telemedicine 'visits' versus education only.
Outcomes	HbA1c and weight.
Notes	There are no data on adherence, although the intervention included 'reinforcement of medication compliance'.

Paes 1997

Methods	- Observational study - Groups clearly defined - Selection bias can be excluded - Losses to follow-up: not described - Duration of follow-up: clear - Confounders: not mentioned and not corrected for - Overall judgement of quality: good
Participants	- 91 type 2 diabetes patients - Multicentre study in an urban area in the Netherlands - Patients recruited in general practice - Sex: F 59.6% - Age: F 70.1 +- 10.7, M: 67.8 +- 11.2 - Treatment modality: oral hypoglycaemic agents
Interventions	To evaluate the impact of dosage frequency - once, twice or three times a day - on the compliance of patients who receive their medicines from community pharmacies.
Outcomes	Compliance with dosage and with prescribed regimen measured with MEMS, pill counts, pharmacy records.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	High risk	

Piette 2001

Methods	- Randomised controlled trial - Adequate randomisation and concealment of allocation - Blinding of patients and administrators: adequate - Adequate blinding of outcome assessment - Description of losses to follow-up and intention-to-treat analysis - Groups were similar at the start of the study - No information on control group care

Piette 2001 *(Continued)*

	- Overall judgement of quality: medium
Participants	- Type 2 diabetes patients recruited in an outpatient setting in a mixed rural and urban area. - Participants: intervention (132), control (140) - sex: intervention (M: 126), control (M: 138) - mean age: intervention (60 yrs, SD 10), control (61 yrs, SD 10) - ethnicity: inter vention (Black: 32, Hispanic 18, Other 11), control (Black 17, Hispanic 16, Other 15) - BMI: intervention (31, SD 7), control (31, SD 6) - HbA1c: intervention (8.2%, SD 1.7), control (8.1, SD 1.7) - serum glucose: intervention (188 mg/dl, SD 94), control (168 mg/dl, SD 68) - all complications: intervention (1), control (0.7) - vascular symptoms: intervention (0.7, SD 0.8), control (0.6, SD 0.8) - treatment modality: insulin: intervention (39), control (31)
Interventions	To evaluate automated telephone disease management with telephone nurse follow-up versus usual care, as a strategy for improving diabetes treatment processes and outcomes.
Outcomes	All diabetes related symptoms, hypo- and hyperglycaemic symptoms, vascular symptoms, HbA1c, serum glucose, self-monitoring frequency, foot inspection, weight monitoring, podiatry visits, ophtalmology visits, diabetic clinic visits, cholesterol tests.
Notes	Inclusion criteria: veterans aged younger than 75, with a life expectancy of more than 12 months, not newly diagnosed type 2 diabetes, and having a touch tone telephone a home.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	

Pullar 1988

Methods	- Randomised controlled trial - Concealment of allocation: data missing - Blinding (patient, administrator, outcome measurement): data missing - losses to follow-up: described - intention-to-treat analysis: unclear - similarity of groups at the start of the study: not mentioned - groups equally provided of care: unclear - overall judgement of quality: poor
Participants	- 179 type 2 diabetes outpatients - Single centre study in a city in the UK. - Age: group 1 (64.9 years +- 8.6), group 2 (63.5 years +- 10.5), group 3 (63.6 years +- 10.1) - Treatment modality: all patients on diet and oral hypoglycaemic agents
Interventions	Comparison of compliance with tablets prescribed once, twice, or three times a day.
Outcomes	Tablet count, phenobarbital LDR (level/dose ratios).
Notes	

Rachmani 2002

Methods	- Randomised controlled trial - Randomisation adequate - Blinding of patients or administrators of treatment: data missing - Unclear blinding of outcome assessors - Data missing on losses to follow-up - Intention-to-treat analysis - Groups were similar at the start of the study and were equally provided of care - Overall judgement of quality: medium
Participants	-Single centre study in Israel - Not clear whehter the patients were recruted in a rural or an urban area. - 142 type 2 diabetes patients: intervention (71), control (70) - Sex: intervention (F: 35, M: 36), control (F: 37, M: 33) - Mean age: intervention (57.4 years), control (56.8 years) - BMI: intervention (28.4), control (28.7) - Systolic blood pressure: internvention (162 mmHg, SD 7.3), control (160 mmHg, SD 6.9) - Diastolic blood pressure: intervention (96 mmHg, SD 2.4), control (95 mmHg, SD 2.0) - High Density Lipoproteines: (intervention 38 mg/dL, SD 3), control (39 mg/dL, SD 4) - Trigycerides: intevention (236 mg/100 ml, SD 42), control (243 mg/100ml, SD 36) - Low Density Lipoproteines: intervention (146 mg/dL, SD 10), control (146 mg/dL, SD 9) - HbA1c: intervention (9.5 %, SD 1.6), control (9.6 %, SD 1.9) - Retinopathy: intervention (11), control (10) - Treatment modality: diet alone (intervention 18, control 16), diet + oral hypoglycaemic agent (intervention 43, control 46), diet + insulin (intervention 10, control 8)
Interventions	To examine whether in comparison to a standard consultation, sharing the therapeutic responsability with patients (involving them in the process of their management by providing them with tools to monitor and supervise the effects of therapy) will improve the outcome.
Outcomes	Total mortality, non-fatal vascular events, cerebrovascular death, non-fatal acute myocardial infarction, non-fatal stroke, coronary artery bypass surgery, HbA1c, BMI, albumin/creatinine ratio, blood pressure, retinopathy and glomerular filtration rate.
Notes	

Rosenkranz 1996

Methods	- Randomised controlled trial - Randomisation adequate - Blinding (patients, administrators, outdome assessors): no - Losses to follow-up: clearly described - Intention-to-treat analysis: unclear - Similarity of groups at the start of the study: not mentioned - Groups were equally provided of care - Overall judgement of quality: medium
Participants	- 113 type 2 diabetes patients - Single centre study with outpatients in a mixed rural and urban area in Germany. - Group A (37), group B (35), group C (31) - Sex: group A (F: 14, M: 23), group B (F: 14, M: 21), group C (F: 12, M: 19) - Duration since diagnosis: group A (<5 years 15, 5-10y: 10, 11-20y: 6, > 20y: 6); group B (<5y: 5, 5-10y: 10, 11-20y: 12, >20y:6); group C: <5 y: 6, 5-10y: 17, 11-20y: 6, >20: 2
Interventions	To investigate whether instantaneous Polaroid fundusphotgraphy during a patient consultation would affect future ophtalmological screening behaviour: picture not shown (A) versus picture shown, explained and handed out (B) versus picture shown, explained but not handed out (C).

Rosenkranz 1996 *(Continued)*

Outcomes	Compliance to ophtalmologist consultation recommendations.
Notes	

Simmons 2000

Methods	- Randomised controlled trial - Adequate randomisation and concealment of allocation - Blinding (patients, administrators, outcome assessors): adequate - Description of losses to follow-up: adequate - Intention-to-treat analysis - Groups were similar at the start of the study - Groups were equally provided of care: unclear - Overall judgement of quality: good
Participants	- 68 type 2 diabetes patients in a multi-centre study in an urban area in New-Zealand - Sex: intervention (F: 25, M: 11), control (F: 23, M: 9) - Age: intervention (55 years +- 11), control (53 years +- 11) - Ethnicity: local (intervention 26, control 25) - Weight: intervention (100,4 kg +- 24.3), control (104.1 kg +- 26.6) - BMI: intervention (37.3 +- 8), control (38.5 +- 10.2) - Systolic blood pressure: intervention (141 mmHg +- 16), control (142 mmHg +- 18) - Diastolic blood pressure: intervention (83 mmHg +- 10), control (80 mmHg +- 9) - HbA1c: intervention (9.9% +- 2.2), control (9.5 % +- 1.7) - Insulin treated: intervention (2), control (5)
Interventions	To assess the impact of calendar blister pack use versus usual delivery of tablets.
Outcomes	HbA1c, blood pressure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	

Skaer 1993

Methods	- Randomised controlled trial - Adequate randomisation - Blinding of patients, administrators and outcome assessors: inadequate - No description of losses to follow-up - Intention-to-treat analysis - Groups were similar at the start of the study - Groups were equally provided of care - Overall judgement of quality: medium
Participants	- Single centre study in the USA - 258 Type 2 diabetes patients recruited from primary care services - Participants : intervention I1 (79), I2 (53), I3 (48), control (78) - Sex: I1 (F: 54, M: 25), I2 (F: 31, M:22), I3 (F:29, M: 19), control (F: 49, M: 29) - Mean age: I1 (53.6 yrs, SD 7.7), I2 (51.8 yrs, SD 8.6), I3 (52.3 yrs, SD 8.4), control (51.7 yrs, SD 7.8)

Skaer 1993 *(Continued)*

	- Treatment modality: oral hypoglycaemic agents: I1: 79, I2: 53, I3: 48, control: 78
Interventions	To discern the effect of mailed prescription-refill reminders (I1), specialised packaging (I2), or a combination of both (I3) on prescription refill compliance and health service utilisation.
Outcomes	MPR (medication prescription refill), number of days' supply obtained over 360 days of the trial.
Notes	Previously untreated type 2 diabetes patients, prescribed glyburide bd, no utilisation of nurse care for prior 3 months.

Smith 1986

Methods	- Randomised controlled trial - Randomisation: adequate - Blinding (patient, administrator, outcome assessor): unclear - Losses to follow-up: described - Intention-to-treat analysis: unclear - Similartity of groups: clear - Groups equally provided of care: unclear - Overall judgement of quality: medium
Participants	- 859 type 2 diabetes outpatients - Single centre study in the USA - Sex: intervention (F: 316, M: 113), control (F: 323, M: 107) - Mean age: intervention (59.3 years +-12.5), control (59.0 yrs +- 13.2) - Ethnicity: intervention (301 Black), control (300 Black) - Systolic blood pressure: intervention (139 mmHg +-22), control (138 mmHg +- 22) - Diastolic blood pressure: intervention (80 mmHg +- 12), control (79 mmHg +- 11) - Random glycaemia: intervention (209 mg/dL +- 94), control (216 mg/dL +- 94) - Treatment modality: oral hypoglycemic agents (intervention: 97, control: 120), insulin (intervention: 328, control: 304), combination (intervention: 4, control: 6)
Interventions	To determine the effect of mailed packets, mailed appointment reminders and intense follow-up of visit failures.
Outcomes	Appointment keeping, prescription refill, walk-in visits, total visits and failure rate.
Notes	

White 1986

Methods	- Randomised controlled trial - Adequate randomisztion - Concealment of allocation: inadequate - Blinding of patient, administrator of treatment, and of outcome assessment: data missing - Losses to follow-up clearly described and intention-to-treat analysis - Groups were similar at the start of the study - Groups were equally provided of care - Overall judgement of quality: poor
Participants	- 32 type 2 diabetes outpatients - Inclusion criteria: less than satisfactory control (FBG >140 mg/dl), infrequent hypoglycaemic reactions (<1/mo), no history of ketoacidosis, body weight >15% above the mean value for height, no history of alcohol abusus or severe personality disorder, and no current use of glucocorticoids. - Sex: men only

White 1986 *(Continued)*

	- Age: intervention (62.4 years +- 5.5), control (60.7 years +- 6.4) - Percentage of weight excess: intervention (36.3% +- 21.0), control (44.3% +- 21.0) - Duration since diagnosis: intervention (10.2 years +- 12.9), control (13.6 years +- 9.6)
Interventions	To compare the effect of group management versus an advice-educational technique.
Outcomes	HbA1c
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allen 1990	No measurement of adherence.
Arauz 2001	No assessment of adherence.
Barcelo 2001	Assessment of dietary adherence only.
Basa 1994	No assessment of adherence.
Benjamin 1999	Assessment of doctors' adherence with standards of care, not of patients with treatment.
Brown 1999	No assessment of adherence.
Cabrera-Pivaral 2000	The effectiveness of an educational program aimed at modifying human behaviors in dietetic habits.
Campbell 1996	Assessment of treatment intensity, not of adherence.
Coleman 1998	No assessment of adherence.
Cooper 1998	No data on adherence.
d'Eramo-Melkus 1992	No assessment of medication adherence.
Day 1992	Asessment of a new integrated system of diabetes care with diabetes nurses, no assessment of adherence to treatment recommendations.
de Grauw 2001	No assessment of an intervention intended to enhance adherence.
de Sonnaville 1997	No assessment of adherence adherence.
Domenech 1995	Judgement of the overall treatment quality, but no assessment of medication adherence.
Estey 1990	Self-monitoring of blood glucose does not count as a medical recommendation.

Study	Reason for exclusion
Fontbonne 1989	No assessment of adherence.
Fritsche 1999	No assessment of adherence.
Greenfield 1994	No measurement of adherence.
Guillausseau 2001	No data on adhernce to treatment recommendations.
Halbert 1999	Not clear whether patients had type 2 diabetes. No real control group.
Hiss 2001	Adherence was not specifically the aim of the intervention, no assessment of adherence.
Hoskins 1988	No assessment of interventions to enhance adherence.
Jirkovska 2000	No assessment of adherence.
Jones 1989	Judging from mean age and number of years since diagnosis: type 1 diabetes patients.
Karter 2001	No intervention. Only characteristics of adherent and non-adherent people were assessed.
Kim 1996	Effect on knowledge, self-control of eating behaviour and coping with stress. No assessment of adherence.
Kinmonth 1998	No assessment of adherence.
Kirkman 1994	Although nurse calls are designed to encourage compliance, no specific measurement is taken. No focus on adherence to medication. Adherence is measured to diet, exercise and quitting smoking only.
Kronsbein 1988	Adherence to glucosuria monitoring instructions.
Lo 1996	No assessment of adherence.
Mazzuca 1986	Authors assessed compliance by questionnaire, but they do not report the results.
McDermott 2001	No assessment of adherence.
Morgan 1988	No assessment of adherence.
Muchmore 1994	Self-monitoring blood glucose and dietary adherence.
Mulrow 1987	Effectiveness of educational intervention in relation to compliance beliefs.
Neumann 1989	No intervention neither a measurement of adherence.
Oi 1998	No assessment of adherence.
Ovhed 2000	No assessment of adherence.
Pieber 1995	No assessment of adherence.
Pill 1998	No assessment of adherence.
Ridgeway 1999	Assessment of changes in medication requirements, not of adherence.

Study	Reason for exclusion
Rubin 1991	Assessment of self-care, not of adherence.
Rutten 1990	No assessment of an intervention aimed at improving adherence, a protocol was studied instead.
Smith 1987	Duplicate publication of Smith DM 1986 (included) whithout any additional information on adherence, but only more data on non-elective hospitalisations.
Tamai 1995	No extractable data.
Trento 2001	No assessment of adherence.
Tu 1993	Study duration only four weeks.
van den Arend 2000	Self-care behaviour was assessed by a self-report questionnaire without any question on medication adherence.
Wedman 1987	No assessment of an intervention aimed at enhancing adherence to treatment recommendations.
Weinberger 1995	Although nurse calls are designed to encourage compliance, no specific measurement for adherence is taken. No focus on adherence to medication.
Whitlock 2000	No assessment of adherence.
Wilson 1987	No assessment of adherence.

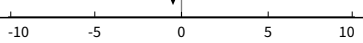
DATA AND ANALYSES

Comparison 1. Education/Facilitation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	9	1192	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.73, -0.25]
1.1 3 months	3	99	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.80, 1.40]
1.2 4 months	3	315	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.79, 0.37]
1.3 6 months	2	71	Mean Difference (IV, Random, 95% CI)	-0.12 [-1.21, 0.98]
1.4 8 months	1	68	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.51, -0.29]
1.5 9 months	1	39	Mean Difference (IV, Random, 95% CI)	0.10 [-1.28, 1.48]
1.6 12 months	3	459	Mean Difference (IV, Random, 95% CI)	-0.83 [-1.75, 0.09]
1.7 48 months	1	141	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.15, -0.25]

Analysis 1.1. Comparison 1 Education/Facilitation, Outcome 1 HbA1c.

Study or subgroup	Education N	Education Mean(SD)	Usual care N	Usual care Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.1.1 3 months							
Mease 2000	15	8.2 (3.5)	13	8.6 (3.4)		0.83%	-0.4[-2.96,2.16]
White 1986	16	8.9 (0.4)	16	10 (0.9)		9.48%	-1.1[-1.58,-0.62]
Krier 1999	21	9.6 (1.9)	18	8.6 (1.9)		3.18%	1[-0.2,2.2]
Subtotal ***	**52**		**47**			**13.5%**	**-0.2[-1.8,1.4]**
Heterogeneity: Tau²=1.47; Chi²=10.28, df=2(P=0.01); I²=80.54%							
Test for overall effect: Z=0.25(P=0.81)							
1.1.2 4 months							
Jaber 1996	17	9.2 (2.1)	22	12.1 (3.7)		1.53%	-2.9[-4.74,-1.06]
Simmons 2000	36	9.1 (2.2)	32	9.1 (1.7)		4.65%	0[-0.93,0.93]
Jiang 1999	121	8.7 (1.4)	87	9 (1.5)		10.75%	-0.3[-0.7,0.1]
Subtotal ***	**174**		**141**			**16.92%**	**-0.71[-1.79,0.37]**
Heterogeneity: Tau²=0.64; Chi²=7.98, df=2(P=0.02); I²=74.93%							
Test for overall effect: Z=1.3(P=0.19)							
1.1.3 6 months							
White 1986	16	9.1 (0.5)	16	9.6 (0.7)		10.43%	-0.5[-0.92,-0.08]
Krier 1999	21	10.5 (2.5)	18	9.8 (2.2)		2.25%	0.7[-0.78,2.18]
Subtotal ***	**37**		**34**			**12.69%**	**-0.12[-1.21,0.98]**
Heterogeneity: Tau²=0.41; Chi²=2.35, df=1(P=0.13); I²=57.45%							
Test for overall effect: Z=0.21(P=0.83)							
1.1.4 8 months							
Simmons 2000	36	9 (0.2)	32	9.4 (0.3)		14.89%	-0.4[-0.51,-0.29]
Subtotal ***	**36**		**32**			**14.89%**	**-0.4[-0.51,-0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.97(P<0.0001)							
1.1.5 9 months							
Krier 1999	21	9.2 (2.5)	18	9.1 (1.9)		2.51%	0.1[-1.28,1.48]
Subtotal ***	**21**		**18**			**2.51%**	**0.1[-1.28,1.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.14(P=0.89)							
1.1.6 12 months							
Coast-Senior 1998	23	8.9 (1.4)	23	11.1 (1.6)		5.09%	-2.2[-3.07,-1.33]
Rachmani 2002	71	8.7 (1.4)	70	9.2 (1.7)		9.01%	-0.5[-1.01,0.01]
Piette 2001	132	8.1 (0.1)	140	8.2 (0.1)		15.38%	-0.1[-0.12,-0.08]
Subtotal ***	**226**		**233**			**29.48%**	**-0.83[-1.75,0.09]**
Heterogeneity: Tau²=0.58; Chi²=24.72, df=2(P<0.0001); I²=91.91%							
Test for overall effect: Z=1.77(P=0.08)							
1.1.7 48 months							
Rachmani 2002	71	8.2 (1.5)	70	8.9 (1.2)		10.01%	-0.7[-1.15,-0.25]
Subtotal ***	**71**		**70**			**10.01%**	**-0.7[-1.15,-0.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.06(P=0)							
Total ***	**617**		**575**			**100%**	**-0.49[-0.73,-0.25]**



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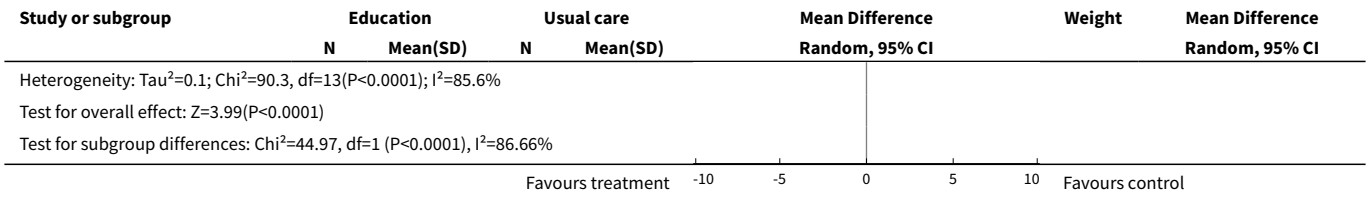
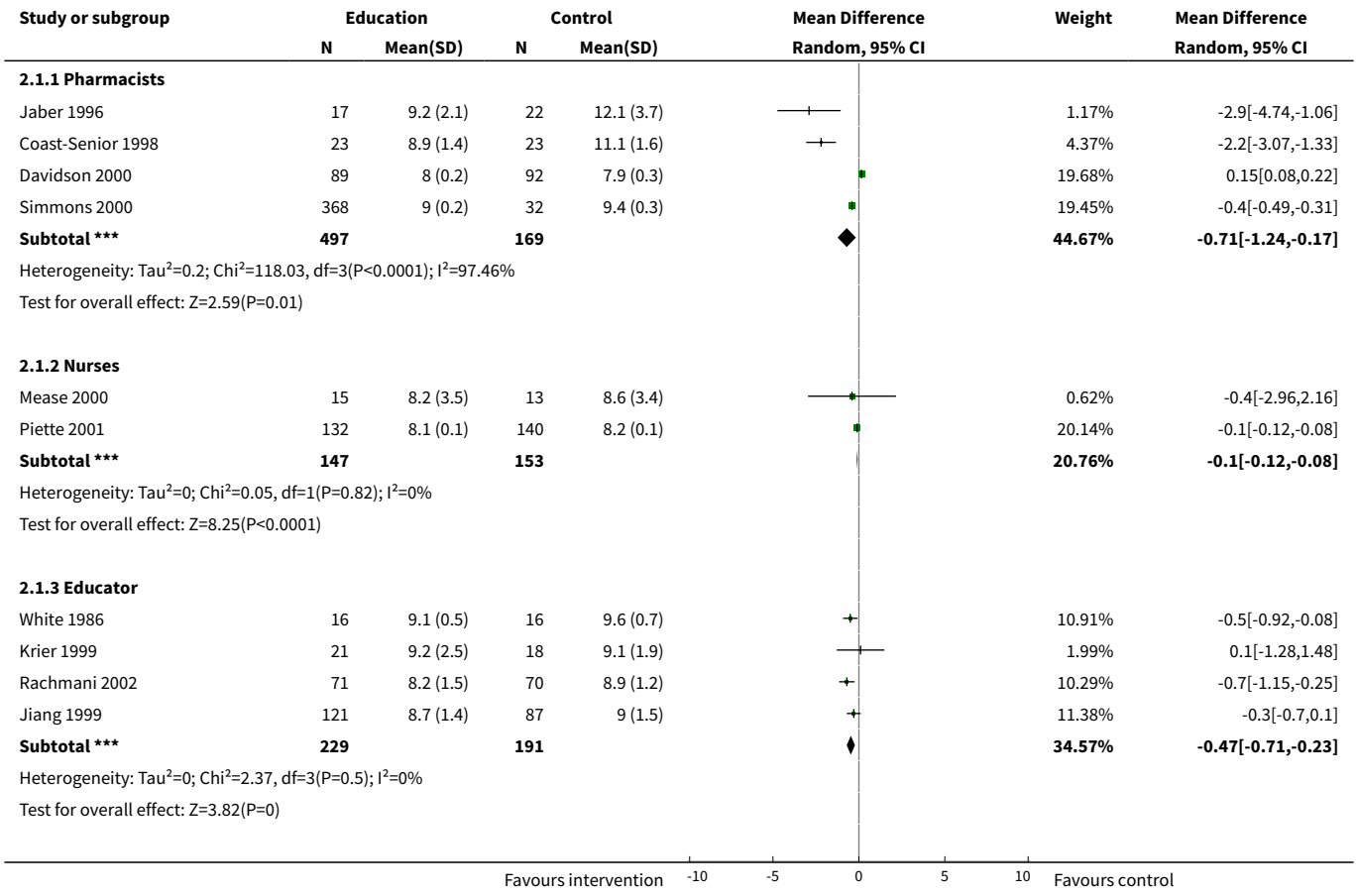
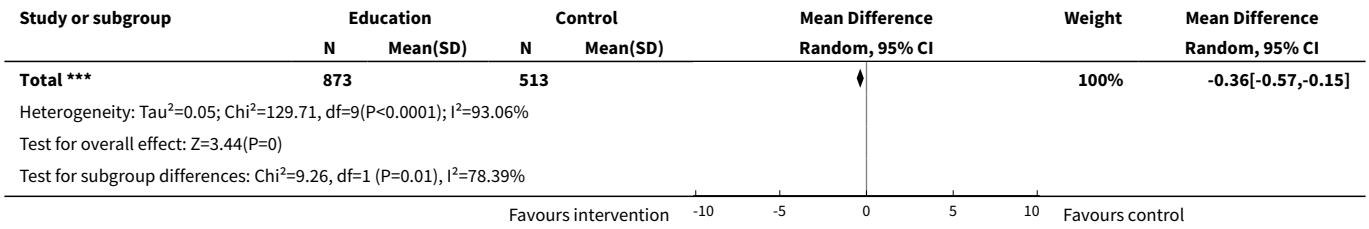


Comparison 2. Educationa/Facilitation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	10	1386	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.57, -0.15]
1.1 Pharmacists	4	666	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.24, -0.17]
1.2 Nurses	2	300	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.12, -0.08]
1.3 Educator	4	420	Mean Difference (IV, Random, 95% CI)	-0.47 [-0.71, -0.23]

Analysis 2.1. Comparison 2 Educationa/Facilitation, Outcome 1 HbA1c.





APPENDICES

Appendix 1. Search strategy

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

TYPE 2 DIABETES MELLITUS

1. See Cochrane Metabolic and Endocrine Disorders Group search strategy.

COMPLIANCE/ADHERENCE

2 Patient compliance [MeSH, all subheadings and categories included]
3 Health behavior [MeSH, all subheadings and categories included]
4 Health education [MeSH, all subheadings and categories included]
5 Self care [MeSH, all subheadings and categories included]
6 Patient education [MeSH, all subheadings and categories included]
7 Patient satisfaction [MeSH, all subheadings and categories included]
8 Educational status [MeSH, all subheadings and categories included]
9 Patient dropouts [MeSH, all subheadings and categories included]
10 Physician-patient relations [MeSH, all subheadings and categories included]
11 Delivery of health care [MeSH, all subheadings and categories included]
12 (health NEAR (behavio*r or education*))
13 (self-care OR self-management)
14 (complianc* OR adherenc*)
15 (patient* NEAR (education* OR satisfaction*))
16 (relationship NEAR (physician* OR doctor*))
17 patient* dropout*
18 treatment* refusal*
19 (empowerment* OR concordanc*)
20 delivery of health care
21 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR#18 OR #19 OR #20

RANDOMISED CONTROLLED CLINICAL TRIALS and CONTROLLED CLINICAL TRIALS

22 See Cochrane Metabolic and Endocrine Disorders Group search strategy

SYSTEMATIC REVIEWS AND META-ANALYSES

23 See Cochrane Metabolic and Endocrine Disorders Group search strategy

ECONOMIC INFORMATION

24 See Cochrane Metabolic and Endocrine Disorders Group search strategy.

(Continued)

TYPE 2 DIABETES AND COMPLIANCE/ADHERENCE AND DIFFERENT STUDY TYPES

25 #1 AND #21 AND (#22 OR #23 OR #24)

WHAT'S NEW

Date	Event	Description
24 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

ETIENNE VERMEIRE: protocol development, literature searches, inclusion/exclusion of studies, quality assessment of trials, data extraction, data analysis, development of final review, corresponding author

JOHAN WENS: protocol development, inclusion/exclusion of studies, quality assessment of studies, data extraction, data analysis, development of final review

PAUL VAN ROYEN: protocol development, inclusion/exclusion of studies, quality assessment and data extraction, co-drafting of the review

HILARY HEARNSHAW: quality assessment and data extraction , co-drafting of review

ANTJE LINDENMEYER: quality assessment and data extraction

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Antwerp, Belgium.

External sources

- Centre for Primary Health Care Studies, University of Warwick, UK.
- Primary Care Diabetes Europe, Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

*Patient Compliance [psychology]; Diabetes Mellitus, Type 2 [psychology] [*therapy]; Health Behavior; Patient Education as Topic; Randomized Controlled Trials as Topic

MeSH check words

Humans