

Patient adherence to medical treatment: a review of reviews

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Abstract

Background

Patients' non-adherence to medical treatment remains a persistent problem. Many interventions to improve patient adherence are unsuccessful and sound theoretical foundations are lacking. Innovations in theory and practice are badly needed. A new and promising way could be to review adherence intervention studies and identify the underlying theories for effective interventions. That is the aim of our study.

Methods

The study is a review of 38 systematic reviews on the effectiveness of adherence interventions published between 1990 and 2005. Electronic literature searches were conducted in Medline, Psycinfo, Embase and the Cochrane Library. Explicit inclusion and exclusion criteria were applied. The scope of the study is patient adherence to medical treatment in the cure and care sector.

Results

Significant differences in the effectiveness of adherence interventions were found in 23 of the 38 systematic reviews. Relatively effective interventions were found in each of four theoretical approaches to adherence interventions: technical, behavioural, educational and multi-faceted or complex interventions. Technical solutions, that is a simplification of the regimen, were often found to be effective, although that does not count for every therapeutic regimen. Overall, our results show that, firstly, there are effective adherence interventions, for example technical solutions, without an explicit theoretical explanation of the operating mechanisms. Secondly, there are effective adherence interventions, incentives and reminders, which clearly stem from the behavioural theories. Thirdly, there are many other theoretical models that seem plausible for explaining non-adherence, but not very effective in improving adherence behaviour. Fourthly, effective components within promising theories, could not be assessed because of the complexity of many adherence interventions and the lack of studies explicitly comparing theoretical components.

Conclusions

Because technical and behavioural interventions to improve adherence often appear to be effective, theoretical developments may benefit from multi-disciplinary collaboration between medical, pharmaceutical, social and, also, technical scientists. The increasing complexity of

interventions hampers theoretical progress and prevents the applicability of interventions in daily clinical practice.

Background

The problem of non-adherence to medical treatment remains a challenge for the medical professions and social scientists. Their efforts to explain and improve patient adherence often appear to be ineffective. Although successful adherence interventions do exist [1-5], half of interventions seem to fail [6] and adherence theories lack sufficient explaining power. As a result of the widespread problem of adherence, substantial numbers of patients do not get the maximum benefit of medical treatment resulting in poor health outcomes, lower quality of life and increased health care costs. [7,8]. In spite of many advances made in adherence research, non-adherence rates have remained nearly unchanged in the last decades [9].

Overviews of the number of non-adherent patients can be found in various reviews [10-14]. DiMatteo found an average non-adherence rate of 24.8% of the patients [13] with the highest rate in patients with HIV, arthritis, gastrointestinal disorders and cancer. The lowest were in patients with pulmonary disease, diabetes and sleep disorders [13]. Measured with Electronic Measurement devices (EM), medication adherence appeared highest in cancer patients (80%), about 75% in many other diseases, for example and cardiovascular, infectious disease and diabetes, and lowest in chronic obstructive pulmonary diseases (COPD) (51%) and asthma (55%) [15]. Cramer found mean adherence rates of 58% and 65% among patients with psychiatric disorders and depression, respectively [11]. In general, adherence rates are higher among patients with acute conditions compared to patients with chronic diseases [16]. Consistent adherence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy [17].

To tackle the problem of non-adherence, innumerable intervention studies have been performed in the last decades [18]. For example, in an attempt to discern effective adherence interventions in cardiac care, two meta-reviews have been published [19,20]. One of these reviews showed that the strongest predictors of adherence were the patients' perception of the strength of a physician's recommendation to attend a rehabilitation programme and the

availability and accessibility of the programme [20]. The other found evidence that simplifying the medication dosage schedules leads to improved adherence [19]. Adherence interventions in various other diseases have also been addressed in a number of systematic reviews. In an extensive review of 153 intervention studies, Roter et al. found that comprehensive interventions were more effective than single, more focused, interventions [21]. Dolder et al. found the same results and concluded that educational interventions were least successful [22]. Indeed, adherence interventions have become increasingly complex and time-consuming [23]. However, even the most effective interventions have only modest effects [24]. The research seems to have come to a dead end [25-28].

One reason for the slow progress in research and development into adherence is the lack of theories to predict and explain non-adherence adequately. Ideally, convincing theories are needed to deduce the potentially effective ingredients of adherence interventions [29]. Moreover, a major problem is the lack of a theoretical basis underpinning adherence interventions [30]. This absence of theoretical foundation impedes our understanding of the disappointing results of many adherence interventions. It also remains unclear whether some theoretical constructs might be more convincing than others in explaining and improving non-adherence [31-33]. As yet, evidence based knowledge is lacking about the most effective, or most promising, theories in adherence research. We will try to deduce this knowledge from effective adherence interventions.

Apart from the search for effective interventions, this study explores which theories deserve to be developed further. The main research questions are:

1. What are the relatively effective adherence interventions and how well do they improve non-adherence?
2. What are the theoretical perspectives that underlie effective adherence interventions and which of them are most promising for further research and development?

The first question will be answered by assessing the relative effectiveness of adherence interventions on the basis of systematic reviews. Regarding the second question, two ways exist to identify the theoretical perspectives underlying adherence interventions. Firstly, in a number of systematic reviews, the adherence interventions are categorized according to the underlying mainstream theories, for example as either behavioural or educational or a combination of both [34-37]. Roter et al. clustered the interventions in four mainstream,

global, theories: behavioural, educational, affective, or combinations of these [21]. By elaborating on their work, we try to analyse further the underlying theoretical principles. Secondly, some interventions are implicitly based on theoretical principles. For example when financial incentives are being used to improve adherence, the underlying theoretical perspective is behavioural because incentives are considered to act as positive reinforcers. Another class of intervention focuses on persuasive communication to improve adherence. As such, communication theories may underpin these interventions. Proceeding along this line of thought, the current study explores which theoretical perspectives, or combination of them, underlie effective adherence interventions.

Methods

Literature search

A systematic literature search was conducted in Medline, Psychinfo, Embase, the Cochrane Library of systematic reviews, and the NIVEL-catalogue, supplemented with manual searches of references. The main keywords were: patient compliance, patient adherence, treatment compliance and treatment drop-outs linked with the keywords, meta-analysis, systematic review and literature review. The searches focused on systematic reviews published between 1990 and March 2005. Systematic reviews were defined as reproducible reviews, based on electronic literature searches and explicit criteria for the selection of the primary studies [38].

Inclusion criteria

The searches yielded a large number of references to adherence reviews. The titles and abstracts of these reviews were screened. From those reviews that seemed potentially suitable, the full text articles in English were obtained and read. Systematic reviews were included if the following selection criteria were met:

- The focus of the review is patient adherence to medical treatment for a diagnosed medical condition prescribed by a health care professional;
- The effectiveness of adherence interventions is a main research question of the review;
- The reviewers conducted and reported electronic literature searches;
- The reviewers applied explicit criteria for the inclusion and exclusion of primary studies;

- The results of the review, that is the effects of adherence interventions, were reported in a quantifiable and tabulated way, for example with effect sizes and odds ratios. All 214 reviews were scored by one reviewer (ES) and independently scored by one of two other reviewers (SvD, LvD). The interrater agreement was 95%. The 5% in which there were disagreements, in total ten reviews, were resolved through discussion. A total of 38 systematic reviews met all the inclusion criteria and were included in the study.

Exclusion criteria

Descriptive reviews were not included in the study. In addition, reviews on the following subjects were excluded:

- Primary prevention and preventive screening of, for example, tuberculosis;
- Population surveys and general health education programmes;
- Phase III clinical trials on new pharmaceuticals and therapies;
- Guideline adherence such as the adherence of health care professionals to protocols or guidelines;
- Reviews reporting only health outcomes without adherence measures.

Data extraction

A data extraction form was used to assess the following characteristics of the reviews: the medical condition or disorder being studied; the type of adherence interventions; the period of literature searches; the number of primary studies; and the total number of patients involved in each review. In addition, we scored whether or not the reviewers had applied criteria concerning:

- randomisation procedures;
- measurements, electronic and otherwise, of adherence;
- minimum sample sizes in the primary studies;
- follow-up periods, in particular minimum ones;
- an analysis of the intention to treat, thereby including patients lost to follow-up;
- rating scales to assess the methodological quality of the primary studies;
- statistical pooling by meta-analytical computations.

A tabulated overview of the details per review is given in Annex 1 as an additional file.

Analysis

The searches yielded a total of 918 references to adherence reviews and a total of 214 reviews seemed potentially suitable. Then, firstly, effective adherence interventions mentioned in the reviews were identified on the basis of statistically significant differences. For this purpose three kinds of reviews were analysed: reviews including single-focused interventions; comparative reviews; and reviews of multiple interventions. We looked too at reviews without significant differences in effect between interventions. We were thereby able to discover whether or not a particular underlying theoretical perspective could explain the lack of significance - and would therefore have to be noted as being less promising. Secondly, we explored the theoretical perspective explicitly or implicitly underlying effective adherence interventions.

Results

Table 1 gives a general overview of the reviews included. The first 12 reviews in the table focus on one single type of adherence intervention, for example technical solutions such as, simplifying dosage or packaging, behavioural interventions, educational interventions, or social support. In the second 13 reviews, two or more types of interventions were analysed in comparison to one another. Most frequently a comparison was made between behavioural, educational, and complex or multi-faceted interventions. Each of the other 13 reviews cover multiple adherence interventions and are not restricted to one special type of intervention.

Table 1

Many adherence interventions appear to be directed at the chronically ill. Twelve reviews concern cardiovascular problems or risks, three diabetes, two asthma/COPD, one haemodialysis and one peptic ulcer. Eight reviews address mental health problems, mainly schizophrenia and depression. Each of the remaining 11 reviews cover various diseases of which two reviews are restricted to the elderly population. Together, the 38 reviews cover 1,373 primary studies (range 4 - 153 studies per review) and 266,988 patients (range 543 – 57,528 patients per review). Twenty-eight of the 38 reviews included were published between 2000 and 2005. Sixteen reviews used meta-analytic computations (see Annex 1 for

further details). In 23 of the 38 reviews, significant differences in the effectiveness of various adherence interventions were found. These were marked with an asterisk (*) in Table 1.

Reviews with significant differences in the effect of different interventions

Technical interventions

Technical adherence interventions, for example on dosage and packaging, are aimed at simplifying the medication regimen. The main adherence interventions in this domain are aimed, firstly, at reducing the number of doses per day, for example through extended release formulations. Secondly, they aim to reduce the number of different drugs in the regimen, for example by using fixed dose combination pills. These are pills that include two or more drugs in fixed proportions in the same formulation or blister packaging of several medications in a fixed combination to be taken together, called unit of use packaging. The theory underlying such interventions is the bio-medical perspective, according to the theoretical analysis of Leventhal et al. [39]. Such ‘technical solutions’ for patients’ adherence problems are characteristic of the bio-medical model. In this model, the medical experts seek solutions for patients’ problems.

The effects on adherence have been assessed in several reviews of single-focused and comparative studies [15,40-44]. Most reviewers arrive at the same conclusion that less frequent dosage results in better adherence. As will be explained below, these results were found in short-term and long-term regimens across a variety of medical disorders and diseases such as peptic ulcer, hypertension, diabetes and cardiovascular disorders. Depression might be an exception to this rule, because the number of anti-depressant drugs was not related to the number of drop-outs in the meta-analysis of Yildiz [44].

Short-term regimen. Buring et al. performed a meta-analysis on adherence to short-term antibiotic regimens, such as those lasting seven days to eight weeks, for peptic ulcer disease caused by *Helicobacter pylori* or *H.pylori* [40]. The number of doses a day of such regimens may range from one to 16. Their analysis of 56 primary studies showed that adherence rates were higher with regimens containing three or fewer doses a day, compared to four to six doses a day ($p=0.001$), seven to eleven ($p=0.009$) or 12 or more ($p<0.0001$). In this study, the magnitude of effect was not mentioned. Adherence may have a significant impact on treatment outcomes. In a study on a triple-drug regimen, significant outcome differences were seen between patients taking less, and those taking more than 60% of their antibiotics. In 90%

of the latter patients *H.pylori* was eradicated successfully, compared to 69% of the other patients [40].

Long-term regimen. Studies on adherence to long-term regimens, defined as ten weeks duration or more, for hypertension were reviewed by Iskedjian et al. [42]. Their meta-analysis showed that the average adherence rate to antihypertension drugs was significantly higher for single daily dosage than for multiple daily dosage (91.4% versus 83.2%, $p < 0.001$). However, the longer the therapy lasted, the lower the adherence rates. For patients taking antihypertensive medication pill organizers and calendar packaging were also found to improve medication adherence [45]. Electronic vial caps improved adherence in a trial among elderly patients. These medication containers display the time when the container was last opened and beep when a dose is due to be taken. The odds ratios in the experimental group were about six times higher than those in the control groups. The intervention was associated with a similar effect on diastolic blood pressure [45].

Various disorders. Adherence measured in a variety of disorders was investigated by Claxton et al. [15]. In their review they only selected studies ($N=76$) that used Electronic Monitoring (EM) devices to measure adherence. Such devices use microprocessors to record the precise time that a dose is removed from the EM unit. Adherence declined as the number of daily doses increased. Adherence to one dose was 79%, two doses 69%, three doses 65% and four doses 51%. Simplification of regimen by unit-of-use packaging also seems to improve adherence, but uncertainty remains about the size of these benefits [41]. All in all there is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence [19] and, where feasible, reducing dose frequency may offer benefits for the patient in terms of health outcomes and costs [43].

Behavioural interventions

The most common behavioural interventions provide patients with memory aids and reminders, whether by mail, telephone, computer, or by home visits. Other classes of interventions consist of monitoring, by means of calendars or diaries, and providing feedback, support or rewards.

Incentives. A clear example of a behavioural approach is using financial incentives to improve adherence [46]. Giuffrida et al. reviewed 11 randomised trials, conducted in the United States,

in which patients were paid for adherence in cash, gifts or vouchers. The incentives ranged from \$5 to gifts worth nearly \$1000. The results showed improved adherence in ten out of 11 studies (Odds ratios > 1.0). It remained unknown whether a cash payment or payment in kind was more effective. The authors argued that incentives can be cost-effective, if substantial benefits accrue, not only to the patient, but also to society at large. An example is to prevent the development of drug-resistant strains of infectious diseases or, in transplant patients, to prevent re-transplantation when patients adhere to their anti-rejection drugs [46].

Reminders. Macharia et al. found that mailed reminders and telephone prompts were consistently useful for reducing the number of missed clinical appointments for the supervised administration of medical care [47]. The conclusions are based on their meta-analytic calculations of 23 randomised trials covering a fairly wide range of interventions and clinical settings. The most common intervention was simply a letter or telephone call a few days prior to the appointment to remind patients of the pending appointment. This proved to be effective in general medical populations (pooled Odds ratio 2.2). According to the authors, computerised reminders can be highly cost-effective. These positive results, however, cannot be safely extrapolated. A telephone-linked reminder system appeared to increase medication adherence among elderly people [48]. The patients in the intervention group had weekly contact with a Telephone-Linked Computer (TCL) system, which questioned them about their medication compliance, adverse drug effects, blood pressure, understanding of their medication regimen, and provided education and motivational counseling to improve medication adherence. Relatively successful strategies in cardiac care were enhancing self-efficacy, skill training and self-monitoring, according to Burke, on the basis of their review of 49 randomised trials [9].

Educational interventions

Educating means teaching, providing knowledge, a cognitive didactic approach. There are many ways to educate patients, for example, individual versus group education, face to face, audio-visually, in writing, by telephone, by e-mail or via home visits. Diabetes education for example most often involves instruction by a multidisciplinary team, including physicians, nutritionists and nurses [49]. Asthma education typically includes a didactic content such as: asking, what is asthma?; coping with stress; self-management of asthma; breathing techniques; and use of medication [50].

Three meta-analytic reviews focused on patient education in relation to chronic diseases. These included both types of diabetes, hypertension and asthma [49-51]. Together they cover 202 primary studies. The authors' main conclusions are that their analyses lend support to the effectiveness of patient education on knowledge, adherence and patient outcome. Knowledge showed the largest effect with a mean effect size of $d_+ 1.05^1$ in diabetes education [49]. The effects of knowledge, however, appear to diminish over time. Measured at two weeks after the intervention, hypertension education showed a large effect size on knowledge of $d_+ 0.98$, but declined to a medium effect size of $d_+ 0.46$ when measured at four weeks [51]. The studies did not include enough data regarding their educational programme to determine what types of programmes and educational strategies are most effective [49]. Educating patients in concrete problem solving and motivational techniques increased medication adherence among schizophrenic patients [52]. In their review of 39 studies, the authors found that 66% of the interventions were unsuccessful. Psycho-educational programmes, although common in clinical practice, were typically ineffective [52]. In addition, education appeared to increase patient adherence in asthma (effect size $d_+ 0.70$) and hypertension (effect size $d_+ 0.49$). In diabetes, adherence to dietary regimens also improved with education (effect size $d_+ 0.57$), but the effects on weight loss were much smaller (effect size $d_+ 0.17$) [49].

Other reviewers found education had positive effects on metabolic control [49], blood pressure [51] and asthma [50]. According to Devine the relatively robust effect of education is probably attributable to the fact that many of the educational programmes included instructions on appropriate medication usage as well as self-care activities [50]. However, Schroeder et al. found that a comparison of four types of adherence interventions among hypertension patients from 38 trials, showed that the most effective one appeared to be dosage simplification [53]. Reducing the number of daily doses of blood pressure lowering medication should be tried as a first line strategy, according to Schroeder, because this appeared to be effective in seven out of nine trials and boosted adherence by eight to twenty percent [53].

A relatively effective adherence intervention in primary care turned out to be collaborative care [54]. Collaborative care was defined as a systematic approach that improves patient education through mental health professionals or other care providers, such as nurses in

¹ The effect size 'd' represents the standardised mean difference between treatment and control groups, measured in standard deviation units. d_+ is the average unbiased weighted effect size.

primary care, playing an active role [54]. Collaborative care was tested against patient education in a review of 19 randomised trials, of which 13 were in primary care. Nine of the 13 primary care studies showed significant differences in adherence between intervention and usual care groups, with an increased adherence of approximately 25%. Better depression outcomes were achieved as well, especially in patients suffering from major depression, who were prescribed adequate dosages of antidepressant medication [54].

Mullen's meta-analysis included 28 controlled trials on cardiac patient education programmes [55]. Patient education was broadly defined and encompassed didactic as well as behavioural approaches. Many cardiac programmes were intensive and consisted of large numbers of contacts, for example in supervised cardiac exercise programmes. The effects were seen in clinical and behavioural outcomes. The average sizes of the effect were 0.51 for blood pressure, 0.24 for mortality, 0.19 for diet and 0.18 for exercise. Smoking cessation and drug adherence did not change significantly. The trend was for behaviorally oriented interventions to have larger effects [55]. However, the difference with didactic interventions did not reach statistical significance, because, according to Mullen, relatively intensive affective interventions were applied in the didactic programmes.

Unfortunately, no comparison of two or more types of interventions was carried out within the studies in order to test the relative effectiveness of different types of interventions [50].

Besides, subgroup analyses or pooling of the results were not always allowed due to the heterogeneity of the samples as defined by Hedges' test of homogeneity. A major weakness of the existing research is under-reporting of key aspects of the studies, for example the duration of the treatment [51].

Social support

A review of DiMatteo addresses the relation between social support and adherence [56].

According to DiMatteo, it is not yet understood how social support contributes to health and which factors moderate and mediate this relationship. Her meta-analysis of 122 studies aimed at assessing which type of social support, either practical, emotional or undifferentiated, has the strongest relationship with adherence [56]. It appeared that practical social support yielded significantly higher effects than emotional and undifferentiated support. The standardized odds Ratio is 3.60 (2.55-5.19). There is a 0.65 SD difference in adherence between patients receiving practical support for their treatment regimen and those not receiving such support.

The risk for non-adherence is almost twice as high among patients who do not receive practical support as among those who do [56].

Structural interventions

An example of a structural or organizational intervention is a programme of care at the place of work to manage hypertension, administered by specially trained nurses [45]. A small but significant improvement in adherence and blood pressure was found. However, additional strategies, such as a disease management programme aimed exclusively at the non-adherent patients, yielded no significant improvements [45]. Another example in this, structural, category consists of community-based rehabilitative intervention programmes for schizophrenic patients [52]. The authors concluded that interventions targeted specifically to non-adherence problems were more likely to be effective (55%) than more broadly based interventions (26%).

Complex or multi-faceted interventions

Among the category of complex interventions, the findings of Haynes et al. deserve special attention [6]. They updated their review of 2002 and added 25 recent studies. They came to three conclusions on the basis of 57 un-confounded randomised trials that reported adherence and treatment outcomes with a follow-up period of at least six months. Firstly, less than half (45%) of the interventions resulted in improved adherence and only 33% in better treatment outcomes. Secondly, those interventions that were effective for long-term care were exceedingly complex and labour-intensive. Thirdly, even the most effective interventions did not lead to large improvements in adherence and treatment outcomes [6].

Roter et al. conducted meta-analytic computations in their review (153 studies) [21]. They found that no single strategy or programmatic focus showed any clear advantage over the other. Comprehensive interventions, combining cognitive, behavioural and affective components, were more effective than single-focused ones (ES 0.34). Affective components concern the provider-patient relationship and refer to issues such as empathy, attentiveness, care, concern or support. The same results were reported by Dolder et al. in a review on schizophrenia [22]. Among schizophrenic patients, interventions of a purely educational nature were the least successful at improving adherence to anti-psychotic medication [22], and behavioural components seem to be needed [57]. The intensity and duration of the interventions did matter, according to Dolder et al. Interventions reporting an improvement in

adherence had a median of eight sessions, while those interventions without gains in adherence had a median of three sessions [22]. Written materials were weaker (ES 0.12) than other educational interventions in Roter's review, but written, mailed, reminders (ES 0.21) were as effective as telephone reminders (ES 0.19) in keeping appointments. All in all, behavioural and educational approaches appeared to be equally effective but Roter et al. suggest that the addition of affective components enhances the effectiveness of the interventions [21]. The variability in study design, along with the multitude of adherence definitions and assessments, precluded reviewers from performing a meaningful meta-analysis [22]. Besides, the differences in adherence measures and definitions of adherence create complications when trying to compare changes in adherence among studies and when calculating mean, non-adherence, rates.

Reviews where there is no significant variation in the effects of different interventions

In fifteen reviews no differences in effectiveness were found. Although some effective interventions were found in most reviews, the reviewers did not find statistical differences between the interventions, or else the authors were reluctant to recommend one intervention over others, due to a lack of evidence. We give some examples.

Overall small effects

No single intervention emerged as a predictor of the overall effect of treatment in four meta-regression analyses [28,35,37,58]. For example, in a thorough meta-analysis (61 studies) Peterson et al. found no significant variation between the different intervention categories. Educational interventions showed an effect size of 0.11, behavioural interventions 0.07, and the combined interventions, 0.08 [35]. Takiya et al. also only found a small and insignificant degree of effect of 0.04 for behavioural interventions in their meta-analytic review of anti-hypertensives (16 studies). Van Dam et al. concluded that patient-focused interventions among people with type 2 diabetes were more effective than provider-focused ones, but the various patient-focused interventions hardly differed in their effectiveness [59]. The meta-analysis of Vermeire et al. (21 trials) showed small effects on a variety of outcomes but no highlights appeared [60]. The authors' conclusion is that: "The 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"

[60]. In four other reviews including, two reviews on hyperlipidaemia [36,61], a review on asthma [34] and a review on medication adherence among the elderly [62], none of the adherence interventions showed significant effectiveness. :

Overlapping components of intervention

The systematic review of Sharp et al. (16 studies) aimed at assessing effective components of psychological interventions in order to improve the adherence of patients receiving haemodialysis [63]. The interventions were based on psychological paradigms and theories. The components of such interventions were intended, for example, to modify health beliefs, apply stages of change theory, self-efficacy training or self-monitoring. The results show that such psychological interventions indicate some success [63]. Superior theories were not found. However, it was not possible, the authors believe, to achieve the review's original aim of examining the efficacy of different intervention components. This was because of the considerable number of components included in any one study and the overlap between the components used in different types of interventions. Therefore it is difficult, according to the authors, to establish the components of treatment responsible for clinical change [63].

Characteristics of reviews both with and without the differences between interventions

Finally, no obvious differences were seen between these 15 reviews, that is those without significant differences, and the other 23 reviews in which significant differences between interventions were found. These two sets of reviews did not differ in respect to the methods applied. In both sets almost half of the reviewers selected only randomised trials (6/15 and 11/23, respectively) and in both sets about 40% of the reviews used meta-analytical computations (6/15 and 10/23, respectively). In addition, no differences were found in the diseases or disorders nor in the theoretical perspectives between the two sets of reviews. There were two differences that did emerge, however. Firstly, only one review in the set of 15 reviews addressed technical solutions, compared to five of the 23 reviews. Secondly, the set of 15 reviews is more recent. Fourteen of the 15 reviews (93%) were published between 2000 and 2005 against 61% in the other set (14/23).

Underlying theoretical perspectives

We found 23 reviews with significant differences between interventions. An overview of the main findings of these reviews are summarized in Table 2. Our first conclusion is that relatively effective adherence interventions were found in each of the four types of adherence interventions: technical, behavioural, educational and multi-faceted or complex interventions. A fifth type, affective interventions, has not been investigated in isolation. Table 2 furthermore shows that technical solutions, mainly simplifying the dosage and packaging, were relatively effective in seven reviews. Behavioural approaches were relatively effective in five reviews, educational approaches in five reviews and complex or multi-faceted interventions in four reviews. The other two reviewers found some evidence for social support [56] and partner-focused strategies [64]. We will now look in more detail on the theoretical principles underlying these adherence interventions. An important observation is that most interventions are eclectic in nature and not strictly representative of one theoretical model. However, some uniformity can be discovered and theoretical constructs can, sometimes, be clearly identified.

Theoretical perspectives underlying technical solutions

Technical adherence interventions imply a simplification of the regimen. There is robust evidence that such simplifications, regarding, for example, dosage and packaging, improve patient adherence. These technical solutions reflect the bio-medical model or perspective [39]. In this model, patients ask for help or advice from medical experts. But what are the origins of this bio-medical perspective? Initially, the bio-medical model sought the reason for non-adherence in, deviant, dispositional characteristics of the patient, for example in personality characteristics or cognitive impairments. However such factors were hardly found [65]. The bio-medical studies found several factors in non-adherence, not related to the individual's character such as the characteristics of the disease, the severity of symptoms and features of treatment or side effects. These findings have motivated the development of technological 'fixes' to enhance compliance [39].

The fact that simplification of regimen improves patient adherence appeals to one's intuition. It seems a practical and logical solution. Theoretically, however, the operating mechanism in

this bio-medical perspective is all but clear. What exactly causes the patient to change his or her behaviour? Is taking one pill so much easier than taking two? According to Claxton et al., the findings reinforce the principle of simplicity [15]. However, no further theoretical explanations were given. Perhaps the lack of a sound explanation is one of the reasons why some reviewers sometimes categorize technical adherence interventions under behavioural approaches [21]. Although the quest for technical solutions is as old as mankind itself, we must confirm that we are unaware of sound theoretical explanations for the effectiveness of simplification. As yet, the bio-medical model does not seem to provide us with causal explanations for patients' behaviour. This seems a first challenge for any development of theory. Perhaps medical and social-psychology scientists should connect with scientists from other fields, for example human engineering, ergonomics, and technical sciences, in order to collaborate in the interests of exploring the theory further.

Theoretical perspectives underlying behavioural interventions

According to our findings, interventions based on reminders and incentives can be successful in improving patient adherence. These interventions represent the powerful principles of behavioural theories. From the perspective of these theories, human behaviour depends on stimuli or cues that elicit certain responses and on the rewards that reinforce behaviour. Reminders can act as cues or stimuli, and incentives as rewards, being all kinds of positive consequences of the behaviour. These are the main, and best known, first principles of behaviour theory. The behaviour may be learned by gradual shaping or forming a pattern of behaviour. Maintenance of the desired behaviour may occur by automation after sufficient repetition, and it may be helpful to avail oneself of behavioural sequences, for example a restructured environment, to elicit responses and provide for rewards [39].

Our findings show that reminders are successful in improving appointment keeping. As such, sending reminders may be considered to be one of the most inexpensive adherence interventions. Increasingly reminders are easy to apply with the help of information technology because computer generated lists of patients can be produced. It should be noted, however, that patients' actual behaviour in taking medication seems less amenable to reminders. This remains a question for future research. Our findings only concern the original basic principles of behaviour theory, stimuli and rewards. Over time, however, the behavioural approaches have been widened. Bandura incorporated principles from social learning theories, for example modeling and vicarious learning, that is learning by watching, listening or reading.

He also added the concept of self-efficacy, the confidence in one's capacity to perform the desired behaviour [66]. Adding these concepts is assumed to make the behavioural approaches more powerful. However, these concepts were not applied in isolation in our sets of reviews and the relative effectiveness of the various components could not be assessed in our data.

Theoretical perspectives underlying educational interventions

Patient education appeared to be relatively successful in five reviews. Education originally refers to a cognitive didactic approach, but nowadays appears to be an overall concept. Educational interventions are defined as any intervention given with the intent of improving the person's ability to manage his or her disease [49]. Behavioural principles, such as reinforcement and feedback, are increasingly incorporated into educational models. Besides, effective education should be tailored to the patient's needs and situation. It should facilitate, be individual and be relevant. It should also ensure that attention is paid to the relationship between the provider and the patient [67]. This makes the concept of patient education a complex one, and one that does not solely refer to a cognitive or didactic theoretical model.

As a result, patient education may contain components of more than one theoretical approach. Unfortunately, we do not know exactly which components contribute to the success of the educational interventions because we do not know which elements were present. Sometimes the content of educational interventions was not described or the descriptions were too broad to deduce the components. For example the interventions made use of patient counseling and self-management programmes. Educational interventions are often denominated by their form and their purposes or goals, more than by their content.

In as far as the patient's education focuses on the transfer of information and knowledge about the disease and its treatment, then the theoretical perspectives can be found in the communication models. These models emphasize conveying the message by trusted and affective messengers (see below). In as far as educational interventions concentrate on changing patients' ideas and perceptions, correct or otherwise, the cognitive models may be the underlying theoretical perspective. The cognitive models emphasize patients' perceptions and beliefs as motivating factors for behaviour. And, as far as educational interventions are aimed at self-management, the underlying perspective may be the self-regulation models. These models emphasize the patients themselves as active problem solvers. In each of these

models various components are incorporated. We will restrict us to a short characterization of the three underlying theoretical approaches, which were originally distinguished by Leventhal et al. in their theoretical analyses [39].

Communication perspective. The communication models focus on the message and the messenger. The patient should be informed adequately. Adequate not only implies that patients understand and retain the message, additional conditions are required for the communication to be effective in changing patients' attitudes and motivations to adhere to the treatment regimen. Patients should believe in the message as well as in the messenger. They should accept the information on the treatment regimen and the benefits of adherence behaviour. The emphasis is on information about 'why' adherence is needed to influence patients' attitudes and motivations. Other factors, external to the message itself, enhance acceptance of the message, such as alliance with the therapist [22] and affective components including for example the practitioner's empathy, friendliness, interest and concern. Additional information can also facilitate behavioural change, for example information about ways to incorporate the behaviour into the patient's daily routines.

Cognitive perspective. The cognitive perspectives focus on cost/benefit analysis as a motivating factor for taking action. For example this action could be within the rational belief model, the health belief model, the theory of reasoned action or planned behaviour. These models assume that health-related behaviour is determined by perceived health threats and the benefits of health behaviour. The basic dimensions of the health belief model are the perceived probability and severity of the threat, on the one hand, and the perceived benefits of health behaviour and the barriers to such behaviour, on the other. Weighing the benefits and barriers and the consequences of various behaviours provides the motivation for the actions to be taken. Such weighing is not based on objective rational computations, but on the individual's own subjective perceptions of the pros and cons. Motivation is also determined by perceived social, group, norms and the perceived social consequences regarding the behaviour and its acceptability.

Self-regulative models. These models emphasize the patients themselves as active problem solvers [68,69]. Patients try to close the gap between the current health status and a goal. In self-regulative models behaviour is considerably influenced by patients' subjective experiences and emotions. Behaviour depends on several factors. These include: the patient's

perceptions of the current status and the goal; the patient's plans for changing the current status to reach the goal, or coping; the patient's appraisal of the progress in reaching the goal. If goals are not reached patients may change their perceptions or the labeling of the status and, or their way of coping. Patients' ways of coping depend on cognitive considerations, for example the perceived identity of health threats and their labeling of the symptoms and potential causes. Parallel to these cognitive processes, emotional reactions may exist and interact. Patients will also label these emotions and their causes, as well as their coping aims to control or diminish often stressful emotions. Both cognitive and emotional ways of coping may be triggered by internal stimuli, for example symptoms, or external ones, such as media messages [39].

In summary, components of these three theoretical approaches are part of an educational approach to 'improve the person's ability to manage his or her disease' [49]. Education often appears to reflect an eclectic approach. From the results of our study it is as yet unclear whether these three theoretical approaches are equally powerful or powerless in improving adherence. Intuitively, each seems to be plausible for explaining adherence behaviour. However, the relative weight of these theories or the effective components in educational interventions designed to improve adherence, could not be assessed.

Discussion

The aim of this study was to explore which adherence interventions, and the underlying theoretical perspectives, are promising for future research and development. Our motive for this study was the slow progress adherence research has made over of thirty years and the disappointing effects of many adherence interventions. Although our study does not allow for firm conclusions, the findings may inspire new directions or ideas. The review studies selected were of a high quality, yet more well-designed studies are needed to formulate robust recommendations [59,70,71]. Comparisons are difficult, due to differences in adherence measures, in interventions and in study populations [72]. More long-term evaluations, in particular, are recommended to establish which interventions maintain their effect over time [58].

The overall results of our study indicate some obvious findings concerning the current adherence interventions and the underlying theoretical perspectives:

- firstly, there are effective adherence interventions, technical solutions, which lack an explicit theoretical explanation of their operating mechanisms;
- secondly, there are effective adherence interventions, such as incentives and reminders, which clearly stem from behavioural theories;
- thirdly, there is a scarcity of comparative studies explicitly contrasting theoretical models or their components.

We observe a knowledge gap between, on the one hand, plausible explanations for non-adherence, and on the other hand, improving adherence behaviour. Explaining non-adherence behaviour does not lead directly to successful interventions for improving adherence. Just as in medical sciences, developments in diagnostics are superior to developments in therapy. A shift in focus seems needed in adherence theories.

A promising new direction in theory development may be found in multi-disciplinary collaboration between traditional adherence experts, from medical, pharmaceutical and social sciences, but also technical scientists. Our findings indicate that technical and practical solutions often lead to successful interventions to improve patient adherence. Although not applicable to any therapeutic regimen, reducing dosage, simplifying packaging or other adaptations, appear to work. Besides, there are indications that structural adaptations in the patient's environment and practical help or support can make it easier for patients to adhere to treatment recommendations. It is perhaps less difficult to change environmental and situational factors than to change the patient. Therefore, we recommend exploring if principles of technical sciences, for example from human engineering or ergonomics, could supplement the theories from medical and social sciences.

Of the behavioural and educational interventions our results indicate that complex and multi-faceted interventions seem to be superior to single focused interventions. However, even those complex interventions appear to result in only small improvements in patient adherence and the outcome of treatment and even complex interventions are ineffective half of the time. This is a matter of great concern. Current adherence interventions are complex and comprehensive and require extra staff and funding. Such time-consuming and costly

interventions are not workable in busy clinical practice. Many review authors therefore recommend the search for simple interventions.

We suggest an additional consideration. Until now, most adherence interventions have involved all patients, both the adherent and non-adherent ones. This may contribute to the confusing and often contradictory research findings. About two thirds of patients spontaneously adhere to treatment recommendations. To them interventions may be a waste of time and money and perhaps affect their autonomy. In our view, interventions should be reserved for patients who need it. An essential prerequisite is therefore the identification of non-adherent patients by health care providers. Unexpected failing in clinical progress could be an indicator. A relevant tool to find out non-adherence may lie in the doctor-patient communication. Doctors should be taught to ask patients routinely and explicitly for their adherence behaviour in a non-threatening and non-blaming way. New communication skills could enable the patient to discuss non-adherence frankly and to express their possible resistance to medication or their barriers to adherence. It is time for doctors and patients to break this 'conspiracy of silence' in the consultation room.

A final observation concerns patient education as an intervention to improve adherence. Such interventions may implicitly be based on several principles derived from various theories. This complicates the identification of effective, theoretical, components. Future theoretical, developments would benefit from a clear conceptual distinction of the theoretical components underlying educational adherence interventions.

An obvious finding in our study is the absence of the patients themselves or patient organisations in the development of adherence interventions. Until now, most adherence interventions have been developed by health care providers and/or social scientists. We recommend to ask patients and patient organisations what exactly would facilitate them to discuss non-adherence openly and what measures would make it easier for patients to adhere. The time has come to involve patients and patient organisations in adherence research and developments.

Conclusion

Theory development may benefit from collaboration between the medical, pharmaceutical, social and technical sciences. The increasing complexity of interventions hampers theoretical progress and prevents the applicability of interventions in daily clinical practice. Progress is also to be expected from identifying effective components within more or less successful interventions.

Competing interests

The authors declare that they have no competing interests. The study was funded by Netherlands Organization for Health Research and Development (ZonMw).

Authors' contributions

JB conceived the study, developed its design and co-ordinated the research team. ES carried out the study and drafted the manuscript together with SvD. The other authors LvD, DdR and RH contributed substantially to the analysis and interpretation of the data and commented on the drafts of the manuscript.

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Table 1. The 38 included reviews and the focus on adherence interventions per review

Interventions	disease/ disorder	technical	behavi oral	educati onal	affecti ve	other	com plex	vari ous
Single focused interventions**)								
Buring SM et al., 1999[40]*	Peptic ulcer	X						
Claxton AJ et al., 2001[15]*	Various	X						
Connor J et al., 2004[41]*	Various	X						
Iskedjian M et al., 2002[42]*	Hypertension	X						
Richter A et al., 2003[43]*	Various	X						
Yildiz A et al., 2004[44]	Depression	X						
Giuffrida A et al., 1997[46]*	Various		X					
Macharia WM et al., 1992[47]*	Various		X					
Brown SA 1990[49]*	Diabetes			X				
Devine EC 1996[50]*	Asthma			X				
Devine EC et al., 1995[51]*	Hypertension			X				
DiMatteo MR 2004[56]*	Various					X ¹⁾		
Comparative interventions**)								
Schedlbauer A et al., 2004[61]	Hyperlipidemia	X		X		X ²⁾	X	
Schroeder K et al., 2004[53]*	Hypertension	X		X		X ³⁾	X	
Merinder LB 2000[57]	Schizophrenia		X	X				
Mullen PD et al., 1992[55]*	Cardiac care		X	X				
Bender B et al., 2003[34]	Asthma		X	X				
Peterson AM et al., 2003[36]	Hyperlipidemia		X	X			X	
Peterson AM et al., 2003[35]	Various		X	X			X	
Takiya LN et al., 2004[37]	Hypertension		X	X			X	
Dolder ChR et al., 2003[22]*	Schizophrenia		X	X	X		X	
Roter DL et al., 1998[21]*	Various		X	X	X	X ⁴⁾	X	
Sharp J et al., 2005[63]	Hemodialysis		X	X	X	X ⁵⁾	X	
Higgins N et al., 2004[62]	Elderly			X			X	
Vergouwen ACM et al.2003[54]*	Depression			X		X ⁶⁾		
Multiple interventions**)								
Burke LE et al., 1997[9]*	Cardiovascular							X
Dodds F et al., 2000[72]*	Psychosis							X
Haynes RB et al., 2005[6]*	Various							X
Morrison A et al., 2000[45]*	Hypertension							X
Newell SA et al., 1999[69]	Cardiovascular							X
Newell SA et al., 2000[64]*	Cardiovascular							X

Nosé M et al., 2003[58]	Schizophrenia							X
Pampallona S et al., 2002[70]	Depression							X
Van Dam HA et al., 2003[59]	Diabetes							X
Vander Wal MHL et al., 2005[71]	Cardiovascular							X
Van Eijken M et al., 2003[48]*	Elderly							X
Vermeire E et al., 2005[60]	Diabetes							X
Zygmunt A et al., 2002[52]*	Schizophrenia							X
Total	38	8	10	15	2	6	8	13

1) social support, 2) intensified care, 3) patient motivation, 4) provider directed interventions, 5) holistic approaches, 6) collaborative care

*) reviews with significant differences between types of adherence interventions

**) Single focused means that the intervention is based on one model or theory; comparative means that two or more single focused interventions are compared in the review; multiple or complex interventions are based on various models/theories

Table 2. Reviewers who found effective adherence interventions

<i>Technical interventions</i>	<i>Behavioral interventions</i>	<i>Educational interventions</i>	<i>Other interventions</i>	<i>Multifaceted/Complex</i>
Buring, 1999[40]	Burke, 1997[9]	Brown, 1990[49]	DiMatteo,2004[56]	Dolder, 2003[22]
Claxton, 2001[15]	Dodds, 2000[72]	Devine, 1995[51]	Newell,2000[64]	Haynes,2005[6]
Connor, 2004[41]	Giuffrida,1997[46]	Devine, 1996[50]		Roter, 1998[21]
Iskedjian, 2002[42]	Macharia, 1992[47]	Mullen,1992[55]**		Vergouwen,2003[54]*
Morrison, 2000[45]	VanEijken,2003[48]	Zygmunt,2002[52]		
Richter, 2003[43]				
Schroeder,2004[53]				
Total 7	Total 5	Total 5	Total 2	Total 4

*) We consider collaborative care to be a multifaceted intervention

***) The intensive cardiac patient education programs could also be considered to be multifaceted or complex

Additional file

Additional file 1 - Patient adherence table

This file gives detailed tabulated information on the included reviews, namely:

- First author
- Publication date
- Disease/disorder
- Period of literature search
- Number of included primary studies
- Total number of patients in the review
- Number of randomized trials
- Type of review (meta analytic computations)
- Adherence interventions
- Results of the review
- Authors' conclusions
- Authors' recommendations for practice
- Authors' recommendations for research
- Authors' other remarks

Additional files provided with this submission:

Additional file 1 : Annex 1 Included reviews.txt : 45Kb

<http://www.biomedcentral.com/imedia/1570005676109382/sup1.TXT>