

Patient adherence to medical treatment reviewed

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ABSTRACT

Background

Patients' non-adherence to medical treatment remains a persistent problem. Many interventions to improve patients' adherence are unsuccessful, often because sound theoretical foundations are lacking. Innovations in theory and practice are needed. A new and promising way could be to review effective adherence intervention studies and identify their underlying theoretical mainstreams. 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 in- and exclusion criteria were applied. Scope of the study is patient adherence to medical treatment in the cure and care sector.

Results

Significant differences in effectiveness of adherence interventions were found in 23 of the 38 systematic reviews. Relatively effective interventions were found in each of four mainstreams of adherence interventions: technical, behavioral, educational and multifaceted or complex interventions. Technical solutions, i.e. simplification of the regimen, have most often been found to be effective, but this cannot be applied to every therapeutic regimen. The overall results of our study indicate the following findings concerning current adherence interventions and the underlying theoretical perspectives. Firstly, there are effective adherence interventions – 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 behavioral theories. Thirdly, there are many other theoretical models which seem plausible for explaining non-adherence, but which seem not to be very powerful in improving adherence behavior. Fourthly, effective components within theories could not be assessed because of the complexity of many adherence interventions and the lack of studies explicitly comparing theoretical components.

Conclusions

Theory developments may benefit from multidisciplinary collaboration between medical, pharmaceutical, social and technical scientists. The increasing complexity of interventions hampers theoretical progress and prevents the applicability of interventions in daily clinical practice as well. We suggest to reserve complex adherence interventions solely for non-adherent patients. Therefore, communication tools should be developed enabling providers to

detect and discuss non-adherence with their patients.

INTRODUCTION

The problem of non-adherence to medical treatment remains a challenge for the medical professions and social scientists. Their efforts to explain and improve a patient's 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 this widespread adherence problem, substantial numbers of patients do not get the maximum benefit of medical treatment - with poor health outcomes, lower quality of life and increased health care costs as a result [7,8].

Adherence can simply be defined as the extent to which patients follow the instructions they are given for prescribed treatments [9]. Adherence should be distinguished from the concept of 'concordance' which was introduced (or reinvented [10]) by the pharmaceutical societies [11]. Concordance means a shared decision-making process between patient and provider, whereas adherence refers to the patient's behavior afterwards, thus after the decisions about treatment have been made [12]. It is undeniable that many patients experience difficulties in following treatment recommendations (WHO). In spite of many advances made in adherence research, non-adherence rates have remained nearly unchanged in the last decades [13].

The extent of non-adherence

Overviews that quantify the extent of non-adherence can be found in a number of reviews [14-18]. DiMatteo compiled 50 years of adherence research from 1948 to 1998. In her meta-analysis of 569 studies she found an average non-adherence rate of 24.8% [17]. She concluded that adherence is highest in patients with HIV-disease, arthritis, gastrointestinal disorders and cancer, and lowest in patients with pulmonary disease, diabetes mellitus and sleep-disorders [17]. Medication compliance, measured by Electronic Measurement devices (EM) was highest in cancer patients (80% compliance), about 75% in many other diseases (cardiovascular, infectious disease, diabetes mellitus etc.), and lowest among COPD patients (51%) and asthma patients (55%) [19]. Cramer found mean adherence rates of 58% and 65% among patients with psychiatric disorders and depression respectively [15]. Adherence rates are typically higher among patients with acute conditions compared to patients with chronic diseases [20]. Consistent adherence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy [21].

The search for effective adherence interventions

To tackle the problem of non-adherence, innumerable intervention studies have been performed in the last decades [22]. Two meta-reviews have been published in search for effective adherence-interventions in cardiac care[23,24]. The strongest predictors of adherence were the patients' perception of the strength of a physician's recommendation to attend a rehabilitation program and the availability and accessibility of the program [24]. An other meta-review found evidence that simplifying medication dosage schedules leads to improved adherence[23]. Adherence interventions in various other diseases have 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 focused interventions [25]. Dolder et al. found the same results and concluded that educational interventions were least successful [26]. Indeed, adherence interventions have become increasingly complex and time-consuming [27]. However, even the most effective interventions have only modest effects [28]. The research seems to be at a dead end [29-32].

One reason for the slow progress in adherence research and development is the lack of theories to predict an explain non-adherence adequately. Ideally, powerful theories are needed to deduce the potentially effective ingredients of adherence-interventions [33]. Moreover, a major problem is the lack of a theoretical basis underpinning many adherence interventions [34]. This lack 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 powerful than others in explaining and improving non-adherence [35-37]. 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.

Research questions

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

1. What are relatively effective adherence interventions and how well do they improve non-adherence?
2. Which theoretical perspectives underlie effective adherence interventions and which theoretical perspectives are 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. In respect with 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 theoretical mainstream, for example as either behavioral or educational or a combination of both [38-41]. Roter et al. clustered the interventions in four global theoretical mainstreams: behavioral, educational, affective or combinations [25]. Elaborating on their work we try to analyze further the underlying theoretical principles. Secondly, some interventions are implicitly based on theoretical principles. Two examples: when financial incentives are being used to improve adherence, the underlying theoretical perspective is behavioral because incentives are considered to act as positive reinforcers. Another class of interventions 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 (combination of) theoretical perspectives 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 [42].

Inclusion criteria

The searches yielded a total of 918 references to adherence reviews. Titles and abstracts were screened. A total of 214 reviews seemed potentially suitable, and 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, i.e. the effects of adherence interventions, were reported in a quantifiable and tabulated way (effect sizes, Odds ratios, etc.).

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% disagreements (10 reviews) were resolved by discussion. A total of 38 systematic reviews met all 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 (e.g. in tuberculosis);
- Population surveys and general health education programs;
- Clinical trials on new pharmaceuticals and therapies (phase III studies);
- Guideline adherence, e.g. 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 under study, 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 in respect of:

- randomization procedures;
- (electronic) measurements of adherence;
- minimum sample sizes in the primary studies;
- (minimum) follow-up periods;
- intention to treat analysis (to deal with 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 additional file).

Analysis

Firstly, the most effective adherence interventions were identified derived from statistical significant differences between interventions. Secondly, we explored the theoretical perspective explicitly or implicitly underlying effective adherence interventions.

Characteristics of adherence interventions

Table 1 gives a general overview of the included reviews. Three kinds of reviews were distinguished: single-focused reviews, comparative reviews and reviews on multiple interventions. The first 12 reviews in the table focus on one single type of adherence intervention, for example technical solutions as simplifying dosing or packaging, behavioral interventions, educational interventions, or social support. In the second 13 comparative reviews two or more types of interventions were analyzed in comparison with one another - most frequently a comparison between behavioral, educational and complex or multifaceted 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 are directed at the chronically ill. Twelve reviews concern cardiovascular problems or risks, three diabetes mellitus, 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). The majority of the included reviews (28/38) was published in the period 2000 to 2005. The remaining 10 were published between 1990 and 2000. Of the 38 reviews, 16 used meta-analytic computations. See Annex 1 for further details.

Finally, in 23 of the 38 reviews, significant differences in effectiveness between adherence interventions were found. We firstly give the results of these 23 reviews and secondly discuss the 15 reviews without significant differences between adherence interventions.

EFFECTIVE ADHERENCE INTERVENTIONS IN SINGLE FOCUSED REVIEWS

Interventions on technical solutions

Technical adherence interventions - for example on dosing and packaging - are aimed at simplifying the medication regimen. The main adherence interventions in this domain are reducing the number of doses per day (for example through extended release formulations), reducing the number of different drugs in the regimen, for example by using fixed dose combination pills (pills that include two or more drugs in fixed proportions in the same formulation) or unit of use packaging (blister packaging of several medications in a fixed combination to be taken together). The underlying theoretical perspective of such interventions is the bio-medical perspective, according to the theoretical analyses of Leventhal et al. [43]. Characteristic of the bio-medical model are 'technical solutions' for patients' adherence problems. In this model, the medical experts seek solutions for patients' problems.

The effects on adherence have been assessed by several reviewers [19,44-48]. All but one of these reviewers arrive at the same conclusion that less frequent dosing 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 (peptic ulcer, hypertension, diabetes mellitus, cardiovascular disorders etc). 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 [48].

Short-term regimen. Buring et al. performed a meta-analysis on adherence to antibiotic regimens for peptic ulcer disease (caused by *Helicobacter pylori*) [44]. The number of doses a day of such – relatively short-term - regimens may range from 1 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 4-11 doses a day. Lowest adherence was seen with 12 or more daily doses. 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 [44].

Long-term regimen. Studies on adherence to long-term regimens for hypertension were reviewed by Iskedjian et al. [46]. Their meta-analysis showed that the average adherence rate to antihypertension drugs was significantly higher for single daily dosing than for multiple daily dosing (91.4% versus 83.2%, $p < 0.001$). They observed, however, that adherence rates and also the differences in these rates appeared to decrease over time with duration of therapy.

Various disorders. Adherence measured in a variety of disorders was investigated by Claxton et al. [19]. In their review they only selected studies (a total of 76 studies) 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 4 doses 51%. Simplification of regimen by unit-of-use packaging also seems to improve adherence, but uncertainty remains about the size of these benefits [45]. All in all there is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence [23] and where feasible, reducing dose frequency may offer benefits for the patient in terms of health outcomes and costs [47].

Behavioral interventions to improve adherence

A variety of behavioral interventions to improve adherence exists. The most common interventions provide patients with memory aids and reminders, whether by mail, telephone, computer or by home visits. Other classes of interventions consist of monitoring (via calendars or diaries) and providing feedback, support or rewards. Sometimes skill building is added and/or tailoring the regimens to patients' daily activities. These interventions reflect the principles of behavior theory. This theory provides the following explanations for human behavior. Behavior depends on stimuli or cues that elicit certain responses, and on the rewards that reinforce behavior. These are the main and best known original principles of behavior theory. The behavior may be learned by gradual shaping or patterning of the behavior. Maintenance of the desired behavior may occur by automation after sufficient repetition, and

it may be helpful to avail of behavior sequences, for example a restructured environment to elicit responses and provide for rewards [43]. Bandura added the concept of self-efficacy, the confidence in one's capacity to perform the desired behavior [49].

Incentives. A clear example of a behavioral approach is using financial incentives to improve adherence [50]. Giuffrida et al. reviewed 11 randomized trials (all 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 10 out of 11 studies (Odds ratios > 1.0). The authors argue 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 retransplantation when patients adhere to their anti-rejection drugs [50].

Reminders. Macharia et al. found that mailed reminders and telephone prompts were consistently useful for reducing the number of missed clinical appointments [51]. The conclusions are based on their meta-analytic calculations of 23 randomized 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, computerized reminders can be highly cost-effective. These positive results however cannot be safely extrapolated to all medical care because, according to the authors, their review only concerned appointments for supervised administration of medical or psychosocial care [51].

Educational interventions to improve adherence

Educating means teaching, providing knowledge; basically it is a cognitive didactic approach. Usually one distinguishes individual versus group education. There are many ways to educate patients, for example face to face, audiovisually, in writing, by telephone, by e-mail or via home visits. Diabetes education for example most often involved instruction by a multidisciplinary team, including physicians, nutritionists and nurses [52]. Asthma education typically included didactic content such as: what is asthma, coping with stress, self-management of asthma, breathing techniques, and use of medication [53].

Educational interventions are defined as 'any intervention given with the intent of improving the persons ability to manage his/her disease, whether it be in the cognitive, psychomotor or affective domains'[52]. Behavioral principles are increasingly incorporated in educational models. According to Mullen, the five principles for effective patient education are: relevance, individualization, feedback, reinforcement and facilitation [54]. Thus the concept of patient education is a complex one and does not solely refer to a cognitive or didactic theoretical model.

Chronic diseases. Three meta-analytic reviews focus on patient education, all in relation to chronic diseases: diabetes mellitus (both types), hypertension and asthma [52,53,55].

Together they cover 202 primary studies. The authors' main conclusions are that their analyses lend support to the effectiveness of patient education on a) knowledge, b) adherence and c) patient outcome.

Knowledge showed the largest effect with a mean effect size of $d_+ 1.05^1$ in diabetes education [52]. Knowledge effects 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 [55].

Patients' adherence improved. Adherence to asthma regimens increased (effect size $d_+ 0.70$) and hypertension patients increased their medication adherence (effect size $d_+ 0.49$). Also adherence to dietary regimens improved according to self reports by diabetic patients (effect size $d_+ 0.57$) but the effects on weight loss were much smaller (effect size $d_+ 0.17$) [52].

Generally small positive effects on clinical outcomes were reported as well in all three reviews. These included effects on metabolic control [52], on blood pressure [55] and on asthmatic episodes [53]. According to Devine the relatively robust effect of education is probably attributable to the fact that many of the educational programs included instructions on appropriate medication usage and self-care activities [53].

Social support and adherence

A review of DiMatteo addresses the relation between social support and adherence [56]. It is not yet completely understood, according to DiMatteo, precisely how social support contributes to health and which factors moderate and mediate this relationship. Her meta-analysis on 122 studies aimed to assess which type of social support has the strongest

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

relationship with adherence: a) practical support, b) emotional support or, c) undifferentiated support [56]. It appeared that practical social support yielded significantly higher effects than emotional and undifferentiated support. The standardized Odds Ratio is 3.60 (2.55-519). 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].

RELATIVELY EFFECTIVE ADHERENCE INTERVENTIONS IN COMPARATIVE REVIEWS

In the 13 comparative reviews (covering 406 primary studies) mutual comparisons were made between two or more types of interventions (see Table 1). Here the reviewers categorized the interventions according to underlying theoretical mainstreams. The most frequent comparison (in 9 reviews) concerns educational, behavioral and other interventions. In six of the 13 reviews significant differences in effectiveness among categories of adherence interventions were found.

Roter et al. conducted meta-analytic computations in their review (153 studies covering various disorders and diseases) [25]. They found that comprehensive interventions - combining cognitive, behavioral and affective components - were more effective than single-focused ones. Affective components concern the provider-patient relation and refer to issues as empathy, attentiveness, care, concern or support. The same results were reported in a review on schizophrenia [26]. Among schizophrenic patients, interventions of a purely educational nature were the least successful at improving adherence to antipsychotic medication [26], and behavioral components seem to be needed [57]. Written materials were weaker than other educational interventions in Roter's review, but written (mailed) reminders were as effective as telephone reminders in appointment keeping. All in all, behavioral 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 [25].

Hypertension. In a comparison of four types of adherence interventions (38 trials) among hypertension patients, the most effective one appeared to be dosing simplification [58].

Reducing the number of daily doses of blood pressure lowering medication, should be tried as first line strategy, according to Schroeder, because this appeared to be effective in seven out of nine trials and boosted adherence by 8-20%. Of the other interventions, less than half of the trials showed an effect on adherence. These other interventions were educational, complex interventions or mixed interventions.

Depression. Another relatively effective adherence intervention in primary care turned out to be collaborative care [59]. Collaborative care was defined as a systematic approach that improves patient education with an active role of mental health professionals or other care providers, such as nurses in primary care [59]. Collaborative care was tested against patient education in a review of 19 randomized trials, of which 13 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 [59].

Cardiac care. Mullen's meta-analysis included 28 controlled trials on cardiac patient education programs [54]. Patient education was broadly defined and encompassed didactic as well as behavioral approaches. Many cardiac programs were intensive and consisted of large numbers of contacts, for example in supervised cardiac exercise programs. Effects were seen in clinical and behavioral outcomes: the average effect sizes 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 [54]. But the difference with didactic interventions did not reach statistical significance, because – according to Mullen – relatively intensive affective interventions were applied in the didactic programs.

RELATIVELY EFFECTIVE INTERVENTIONS IN REVIEWS ON MULTIPLE INTERVENTIONS

In a further 13 reviews (covering 364 primary studies) the interventions were not categorized according to theoretical mainstreams. These reviewers made comparisons between multiple

interventions. In six reviews no significant differences in effectiveness between interventions were found; seven reviewers found potentially useful interventions. An overview of these interventions is given in Table 2. Most authors emphasize, however, that robust evidence of superiority is lacking. We grouped the interventions in five broad categories.

Table 2

Technical. Pill organizers and calendar packaging were found to improve medication adherence among patients taking antihypertensive medication [60]. 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 ratio's 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 [60].

Behavioral. Of the behavioral approaches, reminders were found to be relatively effective in three reviews [13,61,62]. A telephone-linked reminder system appeared to increase medication adherence among elderly people [62]. The patients (in the intervention group) had weekly contact with a Telephone-Linked Computer (TCL) system, which questioned them about their medication compliance, drug adverse effects, blood pressure, understanding of their medication regimen, and provided education and motivational counseling to improve medication adherence. Tailoring was effective in two reviews [61,62]. Relatively successful strategies in cardiac care were self efficacy enhancement, skill training and self monitoring, according to Burke on the basis of their review of 49 randomized trials [13].

Educational. Educating patients in concrete problem solving and motivational techniques increased medication adherence among schizophrenic patients [63]. The authors found that 66% of the interventions were unsuccessful (in their review of 39 studies). Psycho-educational programs, although common in clinical practice, were typically ineffective [63].

Complex or multifaceted interventions. Of the complex interventions category, 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 unconfounded randomized 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 labor-intensive [6]. Thirdly, Haynes' final conclusion is that even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.

Structural interventions: An example of a structural or organizational intervention is a worksite care program to manage hypertension, administered by specially trained nurses [60]. A small but significant improvement on adherence and blood pressure was found. However, additional strategies (a disease management program) aimed exclusively at the non-adherent patients, yielded no significant improvements [60]. Another example in this (structural) category consists of community based rehabilitative intervention programs for schizophrenic patients [63]. The authors concluded that interventions targeted specifically to non-adherence problems were more likely to be effective (55%) than more broadly based interventions (26%).

REVIEWS WITHOUT SIGNIFICANT DIFFERENCES BETWEEN INTERVENTIONS

In eight of the comparative reviews [38-41,57,64-66] and in six of the reviews on multiple interventions no differences in effectiveness were found [67-72]. 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 limited levels of evidence. We give some examples.

Overall small effects

No single intervention emerged as predictor of overall treatment effect in four meta-regression analysis [32,39,41,68]. In a thorough meta-analysis of Peterson et al. only randomized trials were included in a total of 61 studies [39]. The overall effects of adherence interventions appeared to be very small. They found increases in medication adherence of 4-11%. No significant differences between intervention categories were found: educational interventions showed an effect size of 0.11, behavioral interventions 0.07 and combined interventions 0.08 [39]. Takiya et al. found a small non-significant effect size of 0.04 for

behavioral interventions in their meta-analytic review on anti-hypertensives (16 studies). There did not seem to be any particular intervention that made a larger impact on adherence than others [41].

Van Dam concluded that patient-focused interventions (among people with type 2 diabetes mellitus) were more effective than provider-focused ones, but the various patient-focused interventions hardly differed in effectiveness [70]. The meta-analysis of Vermeire (21 trials) showed small effects on a variety of outcomes but no highlights appeared [72]. The author's conclusion is: "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" [72]. In four other reviews, none of the adherence interventions excelled in effectiveness: two reviews on hyperlipidemia [40,65], a review on asthma [38] and a review on medication adherence among the elderly [64].

Overlap of intervention components

The systematic review of Sharp (16 studies) was aimed at assessing effective components of psychological interventions to improve the adherence of patients receiving hemodialysis [66]. The psychological interventions were based on psychological paradigms and theories. Intervention components were for example modifying health beliefs, applying stages of change theory, self efficacy training or self monitoring. The results show that such psychological interventions indicate some success [66]. Superior theories were not found. Although the review originally aimed to examine the efficacy of different intervention components, it was not possible to do this, according to the authors, because of the considerable number of components included in any one study and the overlap between components used in different types of interventions. Therefore it is difficult, according to the author, to establish the components of treatment responsible for clinical change [66].

Methodological issues

Although usually high-quality studies were selected for the reviews, three reviewers claim that more well-designed studies are needed to formulate robust recommendations [67,69,70]. Another reviewer concluded that comparisons were difficult, due to differences in adherence measures, in interventions and in study populations [71]. Some authors argue that more long-

term evaluations are needed to establish which interventions maintain their effect over time [68].

Finally, no obvious differences were seen between these 15 reviews (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 with the applied methods: in both sets almost half of the reviewers only selected randomized 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). There are neither obvious differences in respect with diseases or disorders addressed by the two sets of reviews or in the theoretical orientation. There are two differences between the two sets of reviews. Firstly, only one review in the set of 15 reviews addressed technical solutions (compared to 5 in the set of 23 reviews). Secondly the set of 15 reviews is of more recent date: 14 of the 15 reviews (93%) were published between 2000 and 2005 against 61% in the other set (14/23).

IDENTIFYING UNDERLYING THEORETICAL PERSPECTIVES

This study firstly aimed to identify the most effective adherence interventions. The secondary aim was to explore which theoretical principles are promising for future research and development. Therefore we have now arrived at the question ‘Which theoretical perspectives can be identified in studies on successful adherence interventions?’

A first observation is that 15 review authors could not assess the relatively most effective adherence intervention. The latter reviewers reported that the most effective components could not be assessed because of: methodological limitations of the studies, the complexity and or variety of adherence interventions, the overlapping components in the different interventions and (in some reviews) a limited number of trials on one type of intervention. In both sets of reviews all theoretical mainstreams were (implicitly) present. However, the 15 reviews were of more recent date. Perhaps the recent stricter levels of evidence prevented the authors to assess one intervention being superior to others or to recommend a particular intervention.

There are 23 reviewers who found significant differences between the interventions and who made recommendations on particular types of adherence interventions. An overview of the main findings of these reviews are summarized in Table 3.

Table 3

Our first conclusion is that relatively effective adherence interventions were found in each of the four mainstreams of adherence interventions: technical, behavioral, educational and multifaceted or complex interventions. A fifth mainstream - affective interventions - has not been investigated in isolation.

Table 3 shows that technical solutions – mainly simplifying dosing and packaging – were relatively effective in 7 reviews. Behavioral approaches were relatively effective in 5 reviews, educational approaches in 5 reviews and complex/multifaceted interventions in 4 reviews. The other two reviewers found some evidence for social support [56] and partner-focused strategies [73]. In addition, reviewers – already mentioned in Table 3 - also found some evidence for structural interventions, for example worksite care or community services [60,63,73]. We will now dwell 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.

Technical solutions and biomedical models

Technical adherence interventions imply a simplification of the regimen. There is robust evidence that such simplifications – regarding for example dosing and packaging – improve patients' adherence. These technical solutions reflect the biomedical models or perspective. [43]. In these models, patients ask for help or advice from the medical experts, who seek solutions for patients' problems.

Let us consider the origins of this bio-medical perspective. Initially, the biomedical model sought the reason for non-adherence in (deviant) dispositional characteristics of the patient (for example personality characteristics, cognitive impairments, and so on). These were sought in vain, however, because such factors were hardly found [74]. The bio-medical

studies found several non-dispositional factors in non-adherence, such as: characteristics of the disease, severity of symptoms and features of treatment or side effects. These findings have motivated the development of technological ‘fixes’ to enhance compliance [43].

The fact that simplification of regimen improves patients’ adherence is intuitively appealing. 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 behavior? Is taking one pill so much easier than taking two? According to Claxton et al., the findings reinforce the principle of simplicity [19]. However, no further theoretical explanations were given. Perhaps the lack of sound explaining mechanisms is one of the reasons why some reviewers sometimes categorize technical adherence interventions under the behavioral approaches [25]. 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 seems not to provide us with causal explanations for patients’ behavior. This seems a first challenge for further theory development. Perhaps medical and social-psychology scientists should connect with scientists from other fields (for example human engineering, ergonomics, technical sciences) to collaborate in the interests of further theory exploration.

Behavioral interventions and theories

Our findings of relatively successful adherence interventions fit in the behavior perspective. According to our findings, interventions based on reminders and incentives can be successful in improving patients’ adherence. These interventions represent in fact the powerful principles of behavioral theories. The reminders act as cues or stimuli that elicit certain responses and the incentives act as rewards that reinforce the desired behavior. Incidentally, the term ‘rewards’ should not be taken literally; rewards may be all kinds of positive consequences of the behavior. It may be helpful to avail of situational factors, for example a restructured environment to elicit responses and provide for rewards [43].

Our findings show that reminders are successful in improving appointment keeping. As such, sending reminders may 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 medication taking behavior seems less amenable to reminders. This remains a question for future research.

Our findings only concern the original basic principles of behavior theory, stimuli and rewards. These principles focus directly on patients' non-adherence behavior. Over time, the behavioral approaches have been widened. Bandura incorporated principles from social learning theories, for example modeling and vicarious learning (learning by watching, listening or reading). He also added the concept of self-efficacy, the confidence in one's capacity to perform the desired behavior [49]. Adding these concepts is assumed to make the behavioral 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.

Educational interventions and the underlying perspectives

Patient education appeared to be relatively successful in five reviews. Education originally refers to a cognitive didactic approach. The concept of patient education 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/her disease [52]. Behavioral principles are increasingly incorporated in educational models, for example reinforcement and feedback. Besides, effective education should be tailored to the patient's needs and situation (relevance, individualization and facilitation) and the relationship between provider and patient matters (affective components) [54].

Patient education therefore may contain components of more than one theoretical mainstream. Unfortunately, we do not know which components exactly contributed to the success of the educational interventions because we do not know which elements were present. The educational reviews could not give an indication of the relative weight of the various components, because often details regarding the content of educational interventions were lacking or the descriptions were too broad to deduce the components (for example the interventions made use of patient counseling, self management programs, and so on). Educational interventions are often denominated by their form and their purposes or goals, more than by their content.

As far as patient education focuses on transfer of information and knowledge about the disease and its treatment, the theoretical perspectives can be found in the communication models. These models emphasize conveying the message by trusted and affective messengers (see below). As far as educational interventions concentrate on changing patients' ideas and (mis)perceptions, the cognitive models may be the underlying theoretical perspective. The cognitive models emphasize patients' perceptions and beliefs as motivating factors for behavior. 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 mainstreams, which were originally distinguished by Leventhal et al. in their theoretical analyses [43].

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' attitude and motivation to adhere. 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 behavior. The emphasis is on information about 'why' adherence is needed to influence patients' attitude and motivation. Other factors, external to the message itself, enhance acceptance of the message. For example alliance with the therapist [26]. Affective components are required, particularly a patient's satisfaction with the practitioner (empathy, friendliness, interest, concern). Additional information can facilitate behavior change, for example information about ways to incorporate the behavior into the patient's daily routines.

Cognitive perspective: The cognitive perspectives focus on cost/benefit analysis as a motivating factor to act (Rational belief model, Health Belief model, Theory of Reasoned Action or Planned Behavior). These models assume that health related behavior is determined by perceived health threats and the benefits of health behavior. The well known 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 behavior and the barriers to such behavior on the other hand. Weighing the benefits and barriers and the consequences of various behaviors 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 (acceptability of) behavior.

Self-regulative models: These models emphasize the patients themselves as active problem solvers [75,76]. Patients try to close the gap between the current (health) status and a goal. In self-regulative models behavior is considerably influenced by patients' subjective experiences and emotions. Behavior depends on:

- the patient's perceptions of the current status and the goal;
- the patient's plans for changing the current status to reach the goal (coping);
- the patient's appraisal of the progress in reaching the goal.

If goals are not reached, patients may change their perceptions (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 (the cause of) these emotions, and their coping aims to control or diminish (stressful) emotions. Both cognitive and emotional ways of coping may be triggered by internal stimuli (for example symptoms) or external stimuli (for example media messages) [43].

In summary, components of these three theoretical mainstreams are part of an educational approach to 'improve the person's ability to manage his/her disease' [52]. Education often appears to reflect an eclectic approach. From the results of our study it is as yet unclear whether these three theoretical mainstreams are equally powerful or powerless in improving adherence. Intuitively, each of these theories seems to be plausible for explaining adherence behavior. However, the relative weight of these theories or the effective components in educational interventions to improve adherence could not be assessed.

DISCUSSION AND CONCLUSIONS

A final 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 of thirty years of adherence research 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 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 - without an explicit theoretical explanation of the operating mechanisms;
- secondly, there are effective adherence interventions – incentives and reminders – which clearly stem from the behavioral theories;
- thirdly, there are many other theories which seem plausible for explaining non-adherence behavior, but these theories seem to be less powerful in improving adherence behavior [77].
- fourthly, there is a scarcity of comparative studies explicitly contrasting theoretical models or their components.

Our first conclusion is that there appears to be a knowledge gap between, on the one hand, plausible explanations for non-adherence, and on the other hand, improving adherence behavior. Explaining non-adherence behavior not directly leads to successful interventions to improve 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 multidisciplinary collaboration between traditional adherence experts - from medical, pharmaceutical and social sciences - and technical scientists. Our findings indicate that technical and practical solutions often lead to successful interventions to improve patients' adherence. Although not applicable to any therapeutic regimen, reducing dosing, simplifying packaging or other adaptations appear to work. Besides, there are indications that structural adaptations in patients' environment and practical help or support can make it easier for patients to adhere. It is perhaps less difficult to change environmental and situational factors than to change the patient. Therefore, we recommend to explore if principles of technical sciences, for example from human engineering or ergonomics, could supplement the theories from medical and social sciences.

Of the behavioral and educational interventions our results indicate that complex and multifaceted interventions seem to be superior to single focused interventions. However, even those complex interventions appear to result in only small improvements in patients' adherence and treatment outcome and even complex interventions are ineffective half of the time. This is a point 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 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 behavior 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 (theory) 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 organizations in adherence research. Until now, most adherence interventions have been developed by health care providers and/or social scientists. Although some researchers have investigated patients' reasons for non-adherence, patients seldom participate in the development of adherence interventions. We recommend to ask patients and patient

organizations 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 organizations in adherence research and developments.

Competing interests

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

Authors contributions

JB conceived of the study, developed its design and coordinated the research team. ES carried out the study and drafted the manuscript together with SvD. The other authors DdR, RH and LvD have made substantial contributions tot the analysis and interpretation of the data and commented on the first and second draft of the manuscript.

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

Interventions Authors	Disease/ disorder	technic al	behavi oral	educati onal	affecti ve	other	com plex	vari ous
Single focused interventions								
Buring SM et al., 1999[44]*	Peptic ulcer	X						
Claxton AJ et al., 2001[19]*	Various	X						
Connor J et al., 2004[45]*	Various	X						
Iskedjian M et al., 2002[46]*	Hypertension	X						
Richter A et al., 2003[47]*	Various	X						
Yildiz A et al., 2004[48]	Depression	X						
Giuffrida A et al., 1997[50]*	Various		X					
Macharia WM et al., 1992[51]*	Various		X					
Brown SA 1990[52]*	Diabetes Mellitus			X				
Devine EC 1996[53]*	Asthma			X				
Devine EC et al., 1995[55]*	Hypertension			X				
DiMatteo MR 2004[56]*	Various					X ¹⁾		
Comparative interventions								
Schedlbauer A et al., 2004[65]	Hyperlipidemia	X		X		X ²⁾	X	
Schroeder K et al., 2004[58]*	Hypertension	X		X		X ³⁾	X	
Merinder LB 2000[57]	Schizophrenia		X	X				
Mullen PD et al., 1992[54]*	Cardiac care		X	X				
Bender B et al., 2003[38]	Asthma		X	X				
Peterson AM et al., 2003[40]	Hyperlipidemia		X	X			X	
Peterson AM et al., 2003[39]	Various		X	X			X	
Takiya LN et al., 2004[41]	Hypertension		X	X			X	
Dolder ChR et al., 2003[26]*	Schizophrenia		X	X	X		X	
Roter DL et al., 1998[25]*	Various		X	X	X	X ⁴⁾	X	
Sharp J et al., 2005[66]	Hemodialysis		X	X	X	X ⁵⁾	X	
Higgins N et al., 2004[64]	Elderly			X			X	
Vergouwen ACM et al.2003[59]*	Depression			X		X ⁶⁾		
Multiple interventions								
Burke LE et al., 1997[13]*	Cardiovascular							X
Dodds F et al., 2000[61]*	Psychosis							X
Haynes RB et al., 2005[6]*	Various							X
Morrison A et al., 2000[60]*	Hypertension							X
Newell SA et al., 1999[67]	Cardiovascular							X
Newell SA et al., 2000[73]*	Cardiovascular							X

Nosé M et al., 2003[68]	Schizophrenia							X
Pampallona S et al., 2002[69]	Depression							X
Van Dam HA et al., 2003[70]	Diabetes mellitus							X
Vander Wal MHL et al., 2005[71]	Cardiovascular							X
Van Eijken M et al., 2003[62]*	Elderly							X
Vermeire E et al., 2005[72]	Diabetes mellitus							X
Zygmunt A et al., 2002[63]*	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

Table 2. Potentially useful interventions according to seven review authors

Category	Intervention	Source
Technical	calendar packaging, electronic vial caps, patient cards	Morrison et al., 2000[60]
Behavioral	telephone/mail contact and external cognitive aids	Burke et al., 1997[13]
	self efficacy enhancement, skill training, self monitoring	Burke et al., 1997[13]
	patient tailored interventions, reminder systems	Van Eijken et al., 2003[62]
	individualized behavior tailoring regimes	Dodds et al., 2000[61]
Educational	concrete problem solving strategies, motivational techniques	Zygmunt et al., 2002[63]
Complex	complex combinations	Haynes et al., 2005[6]
	multifaceted interventions	Van Eijken et al., 2003[62]
Structural	worksite care	Morrison et al., 2000[60]
	community based services (supportive/rehabilitative)	Zygmunt et al., 2002[63]
	structural strategies	Newell et al., 2000[73]
Other	compliance therapy	Dodds et al., 2000[61]
	partner-focused strategies	Newell et al., 2000[73]

Table 3 Reviewers who found the following relatively 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[44]	Burke, 1997[13]	Brown, 1990[52]	DiMatteo,2004[56]	Dolder, 2003[26]
Claxton, 2001[19]	Dodds, 2000[61]	Devine, 1995[55]	Newell,2000[73]	Haynes,2005[6]
Connor, 2004[45]	Giuffrida, 1997[50]	Devine, 1996[53]		Roter, 1998[25]
Iskedjian, 2002[46]	Macharia, 1992[51]	Mullen, 1992[54]**		Vergouwen,2003[59]*
Morrison, 2000[60]	VanEijken,2003[62]	Zygmunt,2002[63]		
Richter, 2003[47]				
Schroeder,2004[58]				
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

File name: Patient adherence: Annex1

File format: Table

Title of data: Annex 1.

Description of data

This file gives detailed tabulated information of the include 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>