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## **Patient adherence to medical treatment: a meta review**

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### **With cooperation of the International Expert Forum on Patient Adherence**

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# 1 General 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]. In spite of many advances made in adherence interventions, adherence rates have remained nearly unchanged in the last decades [7].

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 [8,9]. The impact of poor adherence is felt even more as the burden of patients with chronic diseases grows worldwide [10]. Chronic diseases require long-term adherence.

Theoretical models lack sufficient power to predict and explain non-adherence adequately. Many adherence interventions are of an empirical-atheoretical nature and not seldom a matter of trial and error. Innovative theoretical developments are needed to make (scientific) progress [11]. The search for evidence-based potential theoretical constructs is the ultimate aim of our study. This evidence will be derived from adherence intervention studies which are summarized in this article.

## 1.1 Definitions of adherence

Adherence can simply be defined as the extent to which patients follow the instructions they are given for prescribed treatments [12]. This definition was somewhat extended by the WHO as 'the extent to which a person's behavior – taking medication, following a diet and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider' [10].

Adherence should be distinguished from the concept of 'concordance' which was introduced (or reinvented [13]) by the pharmaceutical societies [14]. 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 [15]. The term adherence is intended to be non-judgmental; it is an observation of a fact and not intended to blame the patient [16]. Sometimes, non-adherence is indeed sensible, in order to prevent health damage or harm [7]. And ultimately the patient has a right to refuse treatment and make their own decisions [17,18].

## 1.2 The extent of non-adherence

It is undeniable that many patients experience difficulties in following treatment recommendations [10,19]. Overviews that quantify the extent of adherence abound, to begin with the classic work of Haynes et al. 'Compliance in Health Care' [20]. Recent figures of non-adherence can be found in a number of reviews [21-25]. DiMatteo compiled 50 years of adherence research from 1948 to 1998. She calculated adherence rates in a meta-analysis of 569 studies and found an average non-adherence rate of 24.8% [24]. 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 [24].

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%) [26].

Among patients with psychiatric disorders and depression Cramer found mean adherence rates of 58% and 65% respectively and a mean of 76% adherence among patients with physical disorders [22].

The World Health Organization provided an overview of adherence figures for various medical conditions. In general it was concluded that adherence to long-term therapies in the general population is around 50%, but much lower in developing countries than in western society [10]. Adherence rates are typically higher among patients with acute conditions. Consistent adherence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy [27].

### **1.3 Interventions to improve adherence**

To tackle the problem of non-adherence, innumerable intervention studies have been performed in the last decades [28]. The interventions to improve adherence are diverse in approach and intensity. A number of systematic reviews have addressed their effectiveness. In an extensive review of 153 intervention studies Roter et al. found that comprehensive interventions were more effective than single focused interventions [29]. In the same way Dolder et al. concluded that combined interventions were more effective and that educational interventions were least successful [30]. The results of these and other systematic reviews will be summarized in this report. As such, this study is a review of reviews.

At least two ‘reviews of reviews’ on patient adherence have been published. They address specific diseases [31,32].

Dinnes et al. summarized nine systematic reviews on the effectiveness of cardiac rehabilitation programs. With regard to adherence they looked at patients’ attendance at the cardiac programs. The strongest predictors of adherence were the patients’ perception of the strength of a physician’s recommendation to attend the program and the availability and accessibility of the rehabilitation program [32]. Thus, persuasive communication and facilitating conditions appeared to be effective.

The Technology Evaluation Center reviewed seven systematic reviews (covering 69 primary studies) on interventions to improve adherence in respect of medication for chronic cardiovascular disorders. They found evidence that simplifying medication dosage schedules leads to improved adherence [33]. And again, complex behavioral interventions were more effective than single-strategy interventions. It was not possible – according to the authors – to determine which specific components of these complex strategies resulted in benefits [34].

Adherence interventions have become increasingly complex [35] and time-consuming; however, even the most effective interventions have only modest effects [36]. For example in diabetes education, an additional 24 hours of contact between patient and educator was related to 1% decrease in GHb [37]. Despite the mounting literature, the main questions are still unanswered, ‘what causes non-adherence?’, ‘why is it so difficult for patients to take their medication as prescribed?’ and, ‘why are the effects of interventions to improve adherence still so disappointing?’ The research seems to be at a dead end [38-41].

#### **1.4 The resistant non-adherence issue**

One reason for the slow progress is the lack of comprehensive theoretical frameworks to explain both the reasons for (non-)adherence and the potentially effective ingredients of the proposed interventions [42]. Moreover, a major problem is the lack of a theoretical basis underpinning most adherence interventions and most research on this topic [43]. Seldom are interventions theory-driven. This lack of theoretical foundation impedes our understanding of the disappointing results of most adherence interventions. It also remains unclear whether some theoretical constructs might be more powerful than others in explaining non-adherence [44-46]. Such knowledge would be very helpful for discovering the theoretical principles that are most promising in making a breakthrough in future compliance research. Thus, besides the search for effective interventions we should also explore which theories deserve to be developed further and perhaps may yield new potential adherence interventions in the future.

#### **1.5 Research questions**

This article is firstly a search for the most effective adherence interventions in order, secondly, to deduce promising theoretical principles to explain non-adherence behavior. The main research questions are:

1. What are relatively effective adherence interventions and how well do they improve non-adherence?
2. Which theoretical perspectives can be deduced from these relatively effective adherence interventions and how well do they explain non-adherence?
3. Which interventions and the underlying theoretical perspectives are promising for further research and development?

Although adherence interventions are seldom explicitly theory-driven, the interventions are often implicitly based on theoretical principles or theoretical concepts. Then, underlying theories must be traced back to the characteristics of the interventions themselves. For example, in a number of interventions financial incentives have been used to improve adherence. It is obvious that the underlying theoretical perspective is behavioral because incentives are considered to act as positive reinforcers. The behavioral perspective is also the basis for the use of computerized reminders or the use of signaling electronic devices because these act as cues for medication time i.e. adherence. Another class of interventions focuses on informing and educating patients. The emphasis is on adequate conveying of the message or persuasive communication. As such, communication theories may underpin these interventions. Proceeding along this line of thought, the current study tries to explore which (combination of) theoretical perspectives (implicitly) underlie effective adherence interventions.

This approach is not entirely new. Some authors have preceded us. In reviewing adherence studies, they have tried to characterize the studies as either behavioral or educational or a combination of both [47-50]. Roter et al. clustered the interventions in four categories: behavioral, educational, affective or combinations [29]. These authors used global theoretical concepts. Elaborating on their work, we will try to identify more specific theoretical constructs underlying adherence interventions to discover the most promising ones.

As yet, none of the above-mentioned reviewers has drawn explicit conclusions about the most effective or most promising theories in adherence research. The complexity of many adherence interventions may have prevented such conclusions. It is difficult, according to Dolder et al., to identify the effective components in complex interventions because the

use of multiple strategies may dilute what was originally effective in single strategy interventions [30]. This is particularly a problem since nowadays complex and comprehensive adherence interventions are more the rule than the exception. At the outset we must admit that the complexity of adherence interventions will also complicate our efforts to identify the theoretical perspectives implicitly employed. In our view, however, each effort to come out of the blind alley of adherence research deserves a chance [36].



## 2 Methods

### 2.1 General approach

In this meta-review-project, three steps have been followed. Firstly, computerized literature searches were conducted to find reviews aimed at the effectiveness of adherence interventions. The relative effectiveness of adherence interventions has been analyzed and the results are reported in chapter 4. Secondly, from these relatively effective interventions we explored the underlying theoretical constructs in chapter 5. Thirdly, we invited a panel of international adherence experts to participate in a web-based forum discussion on our findings. The final conclusions and recommendations from this expert forum are summarized in chapter 6.

#### Scope of the study

The area covered in this study comprises medical treatments in the cure and care sector, including medical care, nursing care, pharmaceutical care and mental health care. As such, all medical conditions or disorders are included. Excluded are screening and preventive programs and remedies not prescribed by health care providers.

### 2.2 Literature search

Our study covers the period January 1990 to March 2005 (earlier reviews are already summarized in our bibliography of reviews 1979 –1989 [51]). A systematic literature search was conducted in Medline, Psycinfo, Embase, the Cochrane Library of systematic reviews, and the NIVEL-catalogue. These searches were supplemented with manual searches of references. The main keywords were: patient compliance, patient adherence, treatment compliance, treatment drop-outs linked with the keywords meta-analyses, systematic review and literature review (see Annex 1 for details on search strategies). The searches focused on systematic reviews. Systematic reviews were defined as reproducible reviews, based on comprehensive electronic literature searches and explicit criteria for the selection of the primary studies [52].

### 2.3 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 only included if the following five selection criteria were met:

- The subject 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) (See Annex 2). 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 our study (see Table 1 and Annexes 3 and 4). The remaining reviews were excluded. Annex 5 gives an overview of the excluded reviews and the reasons for exclusion. If reviews meeting our criteria have been missed, we would welcome notification of this.

## 2.4 Exclusion criteria

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

- Primary prevention and preventive screening (tuberculosis);
- Populations 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.

Clearly, health outcomes and health benefits are the ultimate goal of adherence behavior [53]. However, a one-to-one relationship between adherence and outcome does not exist [54-56]. Many other factors are at play and much is still unknown about the extent to which a patient's adherence influences his actual health status [57]. We hold the view that adherence deserves attention on its own. Many medical treatments can only be effective if patients actually take their medication and if they adhere to the medical regimen.

## 2.5 Data extraction

A data extraction form was used to assess (and report) 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 analyses (to deal with patients lost to follow-up);
- rating scales to assess the methodological quality of the primary studies;<sup>1</sup>
- statistical pooling by meta-analytical computations.

The scores per review on these items are reported in the remainder of this report in tabulated form in Tables 3.1 and 3.2.

---

<sup>1</sup> The reviewers differed considerably in the kind of rating scale they used to score the methodological quality of the primary studies they selected. In our sample of 38 reviews, we observe 13 different rating scales. These differences prevent a uniform comparison between the reviews.

## 2.6 Analyses

According to the (theoretical) perspectives, the 38 reviews were clustered in six categories (Table 3.3). This clustering was based on the perspective which the authors of the review themselves ascribed to their review.

1. technical solutions (simplifying packaging, dosage etc);
2. behavioral interventions;
3. educational interventions;
4. affective interventions;
5. multifaceted/complex interventions;
6. other interventions.

The relative effectiveness of these six types of adherence interventions were analyzed in succession. Chapter 4 reports the conclusions of the authors of each review objectively. In Chapter 5, we give our interpretation of the theoretical constructs implicitly underlying effective adherence interventions. Chapter 6 reports the conclusions of the expert forum and their recommendations for future adherence research and developments.

## 2.7 International Expert Forum

An international adherence forum was empanelled. For this forum, the corresponding author of each of the included reviews was invited (see Annex 7). These authors were asked to comment on the main findings of our meta-review. The forum discussion was conducted via a closed-circuit website accessible via a private login-number. The website contained the main findings of our meta review, formulated as propositions. The experts were asked:

- a. whether or not they agreed with our propositions, and why?
- b. to prioritize the propositions in order of importance for future research and development. We compiled a summary of the forum discussion, which was sent back for authorization. Chapter 6 reports the authorized summary of the conclusions and the prioritizing. See Annex 8 for the details of the methods and the evaluation of this web-based forum discussion.



### 3 Overview of included reviews

#### 3.1 Characteristics of the diseases or disorders

The 38 systematic reviews included in this study are listed in Table 3.1 in alphabetical order. The main characteristics of the reviews are: the disorder or disease, the period of literature searches, the number of primary studies included in the reviews and the total number of patients per review.

Table 3.1 Overview of included systematic reviews 1990-2005

Authors	Disease or disorder	Literature search	Number of studies	Number of patients
Bender B, et al., 2003 [47]	Asthma	1992-2003	16	3.606
Brown SA, 1990 [58]	Diabetes mellitus(I and II)	1961-1989	82	5.348
Buring SM, et al., 1999 [59]	Peptic ulcer (H.pylori)	1990-1996	63	5.996
Burke LE, et al., 1997 [7]	Cardiovascular	1977-1997	46	29.485
Claxton AJ, et al., 2001 [26]	Various disorders	1986-2000	76	*
Connor J, et al., 2004 [60]	Various disorders	1966-2003	15	3.561
Devine EC, 1996 [61]	Asthma	1972-1993	31	1.860
Devine EC, et al., 1995 [62]	Hypertension	1965-1993	88	6.581
DiMatteo MR, 2004 [63]	Various disorders	1948-2001	122	12.010
Dodds F, et al., 2000 [64]	Psychotic disorders	1984-1999	8	543
Dolder ChR, et al., 2003 [30]	Schizophrenia	1980-2001	21	2.394
Giuffrida A, et al., 1997 [65]	Various disorders	1966-1997	11	2.721
Haynes RB, et al., 2005 [6]	Various disorders	1967-2004	57	10.010
Higgins N, et al., 2004 [66]	Various disorders (elderly)	1966-2002	7	1.030
Iskedjian M, et al., 2002 [67]	Hypertension	1980-1998	8	11.485
Macharia WM, et al., 1992 [68]	Various disorders	1966-1990	23	5.285
Merinder LB, 2000 [69]	Schizophrenia	1966-1997	19	1.718
Morrison A, et al., 2000 [70]	Hypertension	1965-1999	29	12.835
Mullen PD, et al., 1992 [71]	Cardiac care	1971-1992	28	4.995
Newell SA, et al., 1999 [72]	Cardiovascular	1985-1996	20	4.226
Newell SA, et al., 2000 [73]	Cardiovascular	1985-1996	18	*
Nosé M, et al., 2003 [74]	Schizophrenia / Psychosis	1980-2003	24	3.578
Pampallona S, et al., 2002 [75]	Depression	1990-1999	32	12.454
Peterson AM, et al., 2003 [49]	Hyperlipidemia	1966-2000	4	3.077
Peterson AM, et al., 2003 [48]	Various disorders	1966-2000	61	18.922
Richter A, et al., 2003 [76]	Various disorders	1985-2002	62	*
Roter DL, et al., 1998 [29]	Various disorders	1977-1994	153	57.528
Schedlbauer A, et al., 2004 [77]	Hyperlipidemia	1972-2003	8	5.943
Schroeder K, et al., 2004 [78]	Hypertension	1975-2000	38	15.519
Sharp J, et al., 2005 [79]	Hemodialysis	1970-2003	16	647
Takiya LN, et al., 2004 [50]	Hypertension	1970-2000	16	2.446
Van Dam HA, et al., 2003 [80]	Diabetes mellitus	1980-2001	8	1.940
Vander Wal MHL, et al., 2005 [81]	Cardiovascular	1988-2003	48	*
Van Eijken M, et al., 2003 [82]	Various disorders (elderly)	1975-2001	14	4.196
Vergouwen ACM, et al., 2003 [83]	Depression	1966-2002	19	5.232
Vermeire E, et al., 2005 [84]	Diabetes mellitus	1966-2002	21	4.135
Yildiz A, et al., 2004 [85]	Depression	1976-2000	22	1.710
Zygmunt A, et al., 2002 [86]	Schizophrenia	1980-2000	39	3.972
<b>Total 38</b>	--		<b>1373</b>	<b>266.988</b>

\* total number of patients not calculated

Many adherence interventions are directed at the chronically ill. Of the 38 reviews 12 concern cardiovascular problems or risks: cardiac care (5), hypertension (5) and hyperlipidemia (2). Other chronic diseases are the subject of seven reviews: diabetes mellitus (3), asthma/COPD (2), and one on haemodialysis and one on peptic ulcer. A further eight reviews address mental health problems, mainly schizophrenia and depression. Finally, 11 reviews are not disease specific. They cover various diseases (or the general patient population), of which two reviews are restricted to the elderly population only.

The 38 reviews cover 1,373 primary studies. The mean number of studies per review is 36 (range = 4 - 153 studies). There are two very large reviews with 122 and 153 primary studies respectively [29,63]. The six reviews with less than 10 studies focus on specific diseases with fewer clinical trials on adherence interventions available (for example hyperlipidemia). Other reasons for a limited number of studies per review are the application of very strict inclusion criteria by the reviewer or a restricted time period for the literature searches <sup>1</sup>.

A quarter of a million patients were covered in the reviews (N=266,988 patients in 34 of the 38 reviews; in 4 reviews the total number of patients was not calculated). The mean number of patients in the 34 reviews is 7,853 (range = 543 – 57,528 patients).

Clearly, systematic reviews are of recent date. 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.

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<sup>1</sup> Evidently, some primary studies could have been included in more than one review. However, reviews may distinctly focus on one aspect of adherence behaviour (for example, appointment keeping, drop-out, taking medication) or on one type of adherence intervention (for example medication packaging, financial incentives, patient education, id.). Having different points of view minimizes the doubling between the reviews.

### 3.2 Characteristics of the review methods

Table 3.2 Characteristics of the included reviews

Author	Review method	Electronic literature searches	Adherence Measure	RCT CCT PP*	Rand-omized only	Sample >5 or >10	Inten-tion to treat**	Follow up> 6 months	Rating scale applied
Bender B, et al., 2003[47]	Review	X	X	X					
Brown SA, 1990[58]	Meta	X	X	X					X <sup>1)</sup>
Buring SM, et al., 1999[59]	Meta	X	X		X				
Burke LE, et al., 1997[7]	Review	X	X		X				
Claxton AJ, et al., 2001[26]	Review	X	Only electronic	X					
Connor J, et al., 2004[60]	Review	X	X		X				
Devine EC, 1996[61]	Meta	X	X	X		> 5 p group			
Devine EC, et al., 1995[62]	Meta	X	X	X		> 5 p group			
DiMatteo MR, 2004[63]	Meta	X	X	X		> 10 p group			
Dodds F, et al., 2000[64]	Review	X	X		X	X		X	
Dolder C, et al., 2003[30]	Review	X	X	X		>20 p. sample			
Giuffrida A, et al., 1997[65]	Review	X	X		X				
Haynes RB, et al., 2005[6]	Review	X	X		X		X**	X	
Higgins N, et al., 2004[66]	Review	X	X	X					X <sup>2)</sup>
Iskedjian M, et al., 2002[67]	Meta	X	X	X					X <sup>3)</sup>
Macharia WM, et al., 1992[68]	Meta	X	X		X				
Merinder LB, 2000[69]	Review	X	X	X					X <sup>4)</sup>
Morrison A, et al., 2000[70]	Meta	X	X	X		> 10 p sample	X		
Mullen PD, et al., 1992[71]	Meta	X	X	X		> 10 p group			X <sup>5)</sup>
Newell SA, et al., 1999[72]	Review	X	X		X				X <sup>6)</sup>
Newell SA, et al., 2000[73]	Review	X	X		X				X <sup>6)</sup>
Nosé M, et al., 2003[74]	Meta	X	X	X					
Pampallona S, et al., 2002[75]	Review	X	X	X					
Peterson AM, et al., 2003[49]	Meta	X	X		X	> 10 p group			
Peterson AM, et al., 2003[48]	Meta	X	X		X	> 10 p group			
Richter A, et al., 2003[76]	Review	X	X	X					
Roter DL, et al., 1998[29]	Meta	X	X	X		> 10 p sample			

*To be continued next page*

Author	Review method	Electronic literature searches	Adherence Measure	RCT CCT PP*	Rand-omized only	Sample >5 or >10	Inten-tion to treat**	Follow up> 6 months	Rating scale applied
Schedlbauer A, et al., 2004[77]	Review	X	X		X				X <sup>7)</sup>
Schroeder K, et al., 2004[78]	Review	X	X		X				X <sup>8)</sup>
Sharp J, et al., 2005[79]	Review	X	X	X					X <sup>9)</sup>
Takiya LN, et al., 2004[50]	Meta	X	X		X	> 10 p group			
Van Dam HA, et al., 2003[80]	Review	X	X		X				X <sup>10)</sup>
Van der Wal MHL et al., 2005[81]	Review	X	X	X					
Van Eijken M, et al., 2003[82]	Review	X	X		X	> 50 p sample			X <sup>11)</sup>
Vergouwen ACM, et al. 2003[83]	Review	X	X		X				
Vermeire E, et al., 2005[84]	Meta	X	X	X					X <sup>12)</sup>
Yildiz A, et al., 2004[85]	Meta	X	X	X					
Zygmunt A, et al., 2002[86]	Review	X	X	X					
<b>Total</b>	<b>38</b>	<b>38</b>	<b>38</b>	<b>21</b>	<b>17</b>	<b>12</b>	<b>2</b>	<b>2</b>	<b>13</b>

\* RCT - randomized clinical trial; CCT - controlled clinical trial; PP - pre-posttest clinical trial.

\*\* Intention to treat analysis: drop-outs are assumed to be non-compliant. The number of study-completers is expressed as the proportion of the number allocated to the study arm. Haynes et al., 2005, selected studies with at least 80% follow-up of each group studied [6].

### Frame 3.1 Footnotes: overview of the rating scales used in Table 3.2

- 1) The studies were rated using a scale derived from Sackett and Haynes. The maximum score is 21 points; mean of the included studies is 11.53 points; SD is 3.29; range 5-18 [58].
- 2) The methodological quality of the included studies was judged on the basis of a tool developed by Nichol et al. in 1999 (no composite scores for methodological quality were computed, because 'those scores are often neither valid nor reliable in practice', according to the authors) [66].
- 3) A quality rating was used to select studies for inclusion. The quality checklist was adapted from Haynes et al. Maximum score was 17 points. Included were studies  $\geq 8.5$  points [67].
- 4) A table is presented with methodological characteristics of the included studies (blind rating, intention to treat, drop-outs etc) [69].
- 5) To assess study validity, a coding scheme was used based on the one developed by Sackett and Haynes [71].
- 6) The methodological quality was assessed on eight criteria, largely based on those of Haynes et al. The maximum was 35 points per study. 'Poor' studies (less than 50% of the points) were excluded [72,73].
- 7) Quality assessment of the included RCTs was performed according to the Cochrane Reviewers Handbook of Alderson (2004) [77].
- 8) Studies were assessed according to the Cochrane Handbook. RCT characteristics are presented in descriptive format, due to limited evidence on applying quality scores for individual RCTs [78].
- 9) Study quality of the included studies was graded according to criteria developed by the authors (broadly based on established guidelines for conducting systematic reviews) [79].
- 10) The methodological quality of the included studies was assessed by a modified version of the 19-item Van Tulder criteria list. The maximum score per study is 19 points. The mean score of the studies is 17.3 points (range 13-19 points) [80].
- 11) A data extraction form was used to record the data. The form comprised sections on study methodology based on the Consort list [82].
- 12) To grade the internal validity of the included studies the modified Amsterdam-Maastricht score list for RCTs and CCTs was used that has been adapted by the Dutch Cochrane Centre. Another score form was



used to evaluate the validity of case-control and cohort studies [84].

Of the 38 reviews, 16 used meta-analytic computations. All reviews were based on electronic literature searches and all reviewers only included primary studies if measures of adherence were present<sup>2</sup>.

Additional methodological criteria were applied in a good third of the reviews: 17/38 reviewers only included clinical trials if explicit randomization procedures were applied; 12/38 reviewers only selected primary studies with minimum sample sizes and they excluded studies with (very) small sample sizes. Additional conditions in two reviews were intention-to-treat analyses (to take account of drop-outs or subject-loss) and two reviewers only included studies on chronic diseases if the follow-up period was at least 6 months.

Rating scales were applied by 13 reviewers to assess the methodological quality of the primary studies. A variety of rating scales (or checklists, coding schemes etc.) were used. There are self-developed scales or scales adapted from Haynes, from Nichol, from Alderson, from Van Tulder etc.). The reviewers seldom used such quality ratings as a selection criterion for the inclusion or exclusion of primary studies. The ratings were mostly applied (10/13) to the primary studies already included. According to the authors, such ratings were used for 'a careful appraisal of the results of the reviews'. A minority of the reviewers (3/13) used the quality ratings as a selection criterion and they excluded the low quality studies from their review (studies scoring less than 50% of the rating points were excluded in 3 reviews).

### 3.3 Characteristics of adherence interventions

Table 3.3 gives a general overview of the subjects covered by the reviews. Some reviews focus on specific adherence interventions - for example simplifying dosage; others cover a variety of interventions. A number of reviewers characterized the adherence interventions according to the underlying theoretical perspective as either behavioral or educational, as Table 3.3 shows (it is the reviewer's own denomination of the theoretical perspectives).

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<sup>2</sup> Some reviews addressed more than one subject. For example Pampallona et al. addressed adherence interventions on the basis of randomized trials; additionally they addressed the extent of non-adherence on the basis of epidemiological studies [75]. We did not exclude such double focused reviews because the first part of their review - on adherence interventions - was based on randomized trials.

Table 3.3 Focus on adherence interventions per review

Interventions Authors	Technical solutions	Behav- ioral	Educa- tional	Affective	Other	Multiple/ complex	Various interventions
<b>Single focused interventions</b>							
Buring SM et al., 1999[59]*	X						
Claxton AJ et al., 2001[26]*	X						
Connor J et al., 2004[60]*	X						
Iskedjian M et al., 2002[67]*	X						
Richter A et al., 2003[76]*	X						
Yildiz A et al., 2004[85]	X						
Giuffrida A et al., 1997[65]*		X					
Macharia WM et al., 1992[68]*		X					
Brown SA 1990[58]*			X				
Devine EC 1996[61]*			X				
Devine EC et al., 1995[62]*			X				
DiMatteo MR 2004[63]*					X <sup>1)</sup>		
<b>Comparative interventions</b>							
Schedlbauer A et al., 2004[77]	X		X		X <sup>2)</sup>	X	
Schroeder K et al., 2004[78]*	X		X		X <sup>3)</sup>	X	
Merinder LB 2000[69]		X	X				
Mullen PD et al., 1992[71]*		X	X				
Bender B et al., 2003[47]		X	X				
Peterson AM et al., 2003[49]		X	X			X	
Peterson AM et al., 2003[48]		X	X			X	
Takiya LN et al., 2004[50]		X	X			X	
Dolder ChR et al., 2003[30]*		X	X	X		X	
Roter DL et al., 1998[29]*		X	X	X	X <sup>4)</sup>	X	
Sharp J et al., 2005[79]		X	X	X	X <sup>5)</sup>	X	
Higgins N et al., 2004[66]			X			X	
Vergouwen ACM et al.2003[83]*			X		X <sup>6)</sup>		
<b>Variety of interventions</b>							
Burke LE et al., 1997[7]*							X
Dodds F et al., 2000[64]*							X
Haynes RB et al., 2005[6]*							X
Morrison A et al., 2000[70]*							X
Newell SA et al., 1999[72]							X
Newell SA et al., 2000[73]*							X
Nosé M et al., 2003[74]							X
Pampallona S et al., 2002[75]							X
Van Dam HA et al., 2003[80]							X
Van der Wal MHL et al., 2005[81]							X
Van Eijken M et al., 2003[82]*							X
Vermeire E et al., 2005[84]							X
Zygmunt A et al., 2002[86]*							X
<b>Total</b>	<b>8</b>	<b>10</b>	<b>15</b>	<b>2</b>	<b>6</b>	<b>8</b>	<b>13</b>

\* reviews with significant differences between types of adherence interventions

1) social support

2) intensified care

3) patient motivation

4) provider directed interventions

5) holistic approaches

6) collaborative care

Three kinds of reviews can be distinguished. The first 12 reviews in the table focus on one type of adherence intervention, for example technical solutions as simplifying dosing or packaging (6/12), single educational interventions (3/12), single behavioral interventions (2/12) or other interventions (1/12).

Secondly, in 13 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.

Thirdly, 13 reviews cover a variety of adherence interventions; they are not restricted to one special type of intervention.

Concrete examples of interventions are given in the next section together with their relative effectiveness in improving patient adherence. In 23 reviews, significant differences between types of interventions were found.



## 4 Relatively effective adherence interventions

Following the headings in Table 3, the first section in this chapter reports on the results of the single focused reviews on technical solutions (dosing and packaging), behavioral interventions and educational interventions. The next sections turn to the comparative and multifaceted reviews. The relative effectiveness of the interventions - according to the review authors - will be reported.

N.B. 'single focused' interventions are not identical to 'simple' interventions. A single focused intervention - for example patient education - can be simple (an educational leaflet) or comprehensive (educational leaflet + educational visits + educational video sessions).

### 4.1 Single focused adherence interventions

#### **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 effects on adherence have been assessed by several reviewers [26,59,60,67,76,85]. 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 [85].

#### *Short-term regimen*

Buring et al. performed a meta-analysis on adherence to antibiotic regimens for peptic ulcer disease (caused by *Helicobacter pylori*) [59]. The number of doses a day of such – relatively short-term - regimens may range from 1 to 16. Their analyses 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 [59].

#### *Long-term regimen*

Studies on adherence to long-term regimens for hypertension were reviewed by Iskedjian et al. [67]. Their meta-analyses 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. [26]. 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 (which of course does not necessarily mean that the dose was taken). The reviewers investigated the influence of dose frequency on dose taking (the number of pills) and dose timing (taking the dose within the prescribed time frame). Mean dose taking adherence was 71% and mean dose timing adherence 59%. 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%. The EM unit as such has not been demonstrated to influence adherence. 'Telling patients that their dosing will be monitored is not sufficient to change behavior' [26]. Simplification of regimen by unit-of-use packaging also seems to improve adherence, but uncertainty remains about the size of these benefits [60]. All in all there is consistent and robust evidence that simplifying medication dosage schedules leads to improved adherence [87] and where feasible, reducing dose frequency may offer benefits for the patient in terms of health outcomes and costs [76].

#### **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. Finally, skill building and tailoring the regimens to patients' daily activities are considered to be behavioral in nature. Many behavioral interventions consist of combinations of the activities mentioned here.

Two systematic reviews are confined to single focused behavioral interventions [65,68].

#### *Incentives*

A clear example of a behavioral approach is using financial incentives to improve adherence [65]. 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). At first sight it seems to be turning things upside down to pay patients for taking medication instead of letting them pay for it. However 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 [65].

#### *Reminders*

Macharia et al found that mailed reminders and telephone prompts were consistently useful for reducing the number of missed clinical appointments [68]. The conclusions are based on their meta-analyses of 23 randomized trials of sound scientific merit, covering a fairly wide range of interventions and clinical settings. Adherence rates in these studies ranged from 8% to 94% with a mean of 58%. 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). As an example of the net benefits, the authors calculated that an average

attendance rate of 50% would be expected to increase to 69% after using reminder letters. 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 [68].

### **Educational interventions to improve adherence**

Educating means teaching, providing knowledge; basically it is a cognitive didactic approach. Somewhat broader definitions are used in patient education intervention studies. An example: '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'[58]. There are many ways to educate patients, for example face to face, audiovisually, in writing, by telephone, by e-mail or via home visits etc. Usually one distinguishes individual versus group education. Educational interventions are often denominated by their form and their purposes or goals, more than by their content.

#### *Chronic diseases*

Three meta-analytic reviews focus on patient education, all in relation to chronic diseases: diabetes mellitus (both types), hypertension and asthma [58,61,62]. Together they cover 202 primary studies. Diabetes education most often involved instruction by a multidisciplinary team, including physicians, nutritionists and nurses. Asthma education typically included didactic content such as: what is asthma, coping with stress, self-management of asthma, breathing techniques, and use of medication [61]. A large variety of interventions was seen in the reviews on hypertension [62].

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 [58]. 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 [62]. 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  $d_+ 0.17$ ) [58].

It should be noted that – generally small – positive effects on clinical outcomes were reported as well in all three reviews. These included effects on metabolic control [58], on blood pressure [62] and on asthmatic episodes [61]. 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 [61].

The question as to which educational strategy or intervention components are most effective remained unanswered. Devine et al. [62] found no (statistically significant) differences between various types of education. Such comparisons were not possible in the other two reviews, due to insufficient descriptions of detail about the interventions. According to Brown, the primary studies provided many details on study methods but not on the educational interventions [58].

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<sup>1</sup> 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.

### **Social support and adherence**

A review of DiMatteo addresses social support<sup>2</sup> [63]. 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 relationship with adherence: a) practical support, b) emotional support or, c) undifferentiated support [63]. 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 [63]. She points to the importance of designing interventions that include practical help in the context of an emotionally supportive and cohesive network [63].

## **4.2 Comparison of interventions**

In comparative reviews (13 in total; covering 406 primary studies) mutual comparisons were made between two or more types of interventions (see Table 3). Here the reviewers categorized the interventions according to underlying theoretical mainstreams. The most frequent comparison (in 9 reviews) concerns educational, behavioral and other interventions. The aim of these reviews is to discover the most effective approach or components.

### *Effective intervention components found in six reviews*

In six of the 13 reviews differences in effectiveness among categories of adherence interventions were found (not in the other seven).

Roter et al. conducted an extensive meta-analysis of 153 studies covering various disorders and diseases [29]. They found that comprehensive interventions - combining cognitive, behavioral and affective components - were more effective than single-focused ones.

The same results were reported in a review on schizophrenia [30]. The authors suggest that the addition of affective components enhances the effectiveness of the interventions. Affective components refer to relational issues. Such strategies attempt to influence adherence through appeals to feelings and emotions or social relationships and social support, for example via family support, counseling or supportive home visits [29] or alliance with the therapists in schizophrenia [30]. Among schizophrenic patients, interventions of a purely educational nature were the least successful at improving adherence to antipsychotic medication [30], and behavioral components seem to be needed [69].

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. According to Roter, behavioral and educational approaches appeared to be equally effective [29]. All in all, Roter et al. found weak to moderate statistical effects of adherence interventions and they concluded that "no magic bullets" were discovered [29].

### *Hypertension*

The most effective adherence intervention among hypertension patients appeared to be dosing simplification [78] (38 trials). Reducing the number of daily doses of blood pressure lowering medication, should be tried as first line strategy, according to

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<sup>2</sup> The meta-analysis of DiMatteo examines the correlations between social support and adherence (not on interventions to mobilize social support). This review has been included because this overview would be incomplete without social support.



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 [83]. 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 [83].

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 [83].

### *Cardiac care*

Mullen's meta-analysis included 28 controlled trials on cardiac patient education programs [71]. 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 [71]. 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. Program intensity (contact frequency and total contact hours) was not related to effectiveness; consequently Mullen suggests that it is not the time per se but how it is spent.

### *No differences in effectiveness found in the other seven comparative reviews*

Seven reviewers did not find differences in effectiveness of adherence interventions. In a thorough meta-analysis of Peterson et al. only randomized trials were included in a total of 61 studies [48]. 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 [48]. Of the behavioral interventions, mail reminders had the largest impact, with an effect size of 0.38, followed by skill building (0.17), packaging changes (0.14), and dosage schedule change (0.12). Note that dosing and packaging were categorized by Peterson as behavioral interventions.

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 [50].

The systematic review of Sharp (16 studies) was aimed at assessing effective components of psychological interventions to improve the adherence of patients receiving hemodialysis [79]. The psychological interventions were based on psychological paradigms and theories.

Intervention components were:

- token economies;
- behavioral contracting;
- modifying health beliefs;
- applying stages of change theory;
- self regulation;
- self efficacy training;
- self monitoring;
- cognitive therapy;
- social reinforcement;
- skills training;
- stress management.

The results show that such psychological interventions indicate some success [79]. 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 to establish the components of treatment responsible for clinical change [79].

In four other reviews, none of the adherence interventions excelled in effectiveness: two reviews on hyperlipidemia [49,77], a review on asthma [47] and a review on medication adherence among the elderly [66].

### **4.3 Variety of adherence interventions**

In a further 13 reviews (covering 364 primary studies) the interventions were not categorized according to theoretical mainstreams. These reviewers made comparisons between a number of particular interventions. The aim is again to discover the most effective ones. Of the 13 reviewers, six did not but seven did discover some relatively effective interventions. We will firstly turn to the relatively effective interventions.

#### *Relative effectiveness of interventions found in seven reviews*

Seven reviewers gave indications of relatively effective interventions. They emphasize however that robust evidence is lacking. Their conclusions are tentative and the authors mostly consider the selected interventions potentially useful or ‘promising’ at best. An overview of these interventions is given in Table 4.1. We grouped the interventions in five broad categories.

Table 4.1 Potentially useful interventions according to seven review authors

Category	Intervention	Source
Technical	calendar packaging, electronic vial caps, patient cards	Morrison et al., 2000[70]
Behavioral	telephone/mail contact and external cognitive aids self efficacy enhancement, skill training, self monitoring patient tailored interventions, reminder systems individualized behavior tailoring regimes	Burke et al., 1997[7] Burke et al., 1997[7] Van Eijken et al., 2003[82] Dodds et al., 2000[64]
Educational	concrete problem solving strategies, motivational techniques	Zygmunt et al., 2002[86]
Complex	complex combinations multifaceted interventions	Haynes et al., 2005[6] Van Eijken et al., 2003[82]
Structural	worksite care community based services (supportive/rehabilitative) structural strategies	Morrison et al., 2000[70] Zygmunt et al., 2002[86] Newell et al., 2000[73]
Other	compliance therapy partner-focused strategies	Dodds et al., 2000[64] Newell et al., 2000[73]

#### *Technical*

Pill organizers and calendar packaging were found to improve medication adherence among patients taking antihypertensive medication [70]. 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 [70].

#### *Behavioral*

Of the behavioral approaches, reminders were found to be relatively effective in three reviews [7,64,82]. A telephone-linked reminder system appeared to increase medication adherence among elderly people [82]. 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 [64,82]. 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 [7].

#### *Educational*

Educating patients in concrete problem solving and motivational techniques increased medication adherence among schizophrenic patients [86]. 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 [86].

#### *Multifaceted/complex*

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]. Superior interventions were not found. The authors remarked that 'If there is a common thread to these interventions, it is the more frequent interaction with patients with attention to adherence'. Some examples of fairly complex interventions are given in Frame 4.1 below, also to illustrate that the working components in such interventions cannot be disentangled.

Thirdly, Haynes' final conclusion is that even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. According to Haynes, 'high priority should be given to fundamental and applied research concerning innovations to assist patients in following medication prescriptions for long-term medical disorders' [6].

#### Frame 4.1 Two examples of fairly complex interventions [6].

An intervention for hypertension patients included care provided at the worksite, special pill containers, counseling, reminders, self monitoring, support groups, feedback and reinforcement (all administered by staff who were supported from study funds). Positive effects were found on both adherence and patient outcome.

A program for depressed patients involved patient instruction (book and videotape), two visits to a depression specialist, three telephone visits over a period of one year (aimed at enhancing adherence to antidepressant medications, monitoring of symptoms and development of a written relapse prevention plan), four personalized mailings at two, six, 10 and 12 months, and telephone follow-up assessments at three, six, nine and 12 months. Patients in the intervention group had significantly fewer depressive symptoms, but did not have fewer episodes of relapse or recurrence of depression.

#### *Structural interventions*

An example of structural or organizational intervention is a worksite care program to manage hypertension, administered by specially trained nurses [70]. 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 [70]. Another example in this (structural) category consists of community based rehabilitative intervention programs for schizophrenic patients [86]. The authors concluded that interventions targeted specifically to non-adherence problems were more likely to be effective (55%) than more broadly based interventions (26%).

#### *Six reviews did not find relatively effective interventions*

Finally in a further six reviews (of which two meta-analyses), conclusions on the most effective adherence interventions were not drawn [72,74,75,80,81,84]. Of these reviews, two focus on diabetes mellitus and the other ones on cardiovascular problems, heart failure, depression and psychosis respectively.

Although some effective interventions were found in most reviews, sufficient evidence was lacking to recommend one intervention over others. Van Dam concluded that patient-focused interventions were more effective than provider-focused ones, but the various patient-focused interventions hardly differed in effectiveness [80].

No single intervention emerged as predictor of overall treatment effect in a meta-regression analysis of 24 studies [74]. Besides, according to the authors, more long-term evaluations are needed to establish which interventions maintain their effect over time [74]. In another review of 48 studies, comparisons were difficult, due to differences in interventions, study populations and adherence measures [81].

Although usually high-quality studies were selected for the reviews, three reviewers claim that more well-designed studies are needed to formulate robust recommendations [72,75,80].

The meta-analysis of Vermeire (21 trials among people with type 2 diabetes mellitus) showed small effects on a variety of outcomes but no highlights appeared [84]. 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" [84].



## 5 Exploration of theoretical principles

This study is an attempt to find relatively effective theories to explain non-adherence behavior. The second research question is: ‘Which theoretical perspectives can be identified in studies on successful adherence interventions?’ The aim is to explore which theoretical principles are promising for future research and development. In this section we will try to identify which theoretical constructs underlie successful adherence interventions. To this end, the main findings of relatively successful adherence interventions will be summarized first.

### 5.1 Relatively effective adherence interventions

Of the 38 reviews included in this study, 23 reviewers did find indications of relatively effective adherence interventions in comparison with one another. The remaining 15 reviewers concluded that statistically significant differences between adherence interventions did not exist. They could not point to one type of adherence intervention being superior to others.

Table 5.1 Overview of 15 reviews without and 23 reviews with significant differences between adherence interventions

15 reviews without significant differences between interventions				
Bender, 2003 (asthma) [47]			Schedlbauer, 2004 (hyperlipidemia) [77]	
Higgings, 2004 (elderly) [66]			Sharp, 2005 (hemodialysis) [79]	
Merinder, 2000 (schizophrenia) [69]			Takiya, 2004 (hypertension) [50]	
Newell, 1999 (cardiovascular) [72]			Van Dam, 2003 (diabetes mellitus) [80]	
Nosé, 2003 (schizophrenia) [74]			VanderWal, 2005 (cardiovascular) [81]	
Pampallona, 2002 (depression) [75]			Vermeire, 2005 (diabetes mellitus) [84]	
Peterson, 2003 (hyperlipidemia) [49]			Yildiz, 2004 (depression) [85].	
Peterson, 2003 (various disorders) [48]				
23 reviewers who found the following relatively effective adherence interventions				
Technical interventions	Behavioral interventions	Educational interventions	Other interventions	Multifaceted/Complex
Buring, 1999[59]	Burke, 1997[7]	Brown, 1990[58]	DiMatteo,2004[63]	Dolder, 2003[30]
Claxton, 2001[26]	Dodds, 2000[64]	Devine, 1995[62]	Newell,2000[73]	Haynes,2005[6]
Connor, 2004[60]	Giuffrida, 1997[65]	Devine, 1996[61]		Roter, 1998[29]
Iskedjian, 2002[67]	Macharia, 1992[68]	Mullen, 1992[71]**		Vergouwen,2003[83]*
Morrison, 2000[70]	VanEijken,2003[82]	Zygmunt,2002[86]		
Richter, 2003[76]				
Schroeder,2004[78]				
<b>Total 7</b>	<b>Total 5</b>	<b>Total 5</b>	<b>Total 2</b>	<b>Total 4</b>

\* We consider collaborative care to be a multifaceted intervention

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

#### *The 15 reviews without significant differences between interventions*

There are 15 reviews without statistically significant differences between interventions. In each of these 15 reviews some effective patient-focused adherence interventions were

found (this should be kept in mind). The reviewers, however, did not find sound evidence of a particular intervention being superior to other ones. Statistically significant differences between the interventions did not show up. According to three reviewers, methodological limitations prevented strong recommendations. Other reasons given by the authors were: the variety of adherence interventions (2 reviewers), the overlapping components in the different interventions (1 reviewer) and the limited number of studies on one type of intervention (1 reviewer). A comparison between these 15 reviews and the other 23 is described in Frame 5.1 below.

#### Frame 5.1 Comparison between the two sets of reviews (15 and 23)

No obvious differences between the two sets of reviews were seen in the topics of the reviews. In the set of 15 reviews, various diseases were covered: Cardiovascular (2), Diabetes mellitus (2), Hyperlipidemia (2), Depression (2), Schizophrenia (2), Various Disorders (2), Asthma (1) Hemodialysis (1) Hypertension (1).

There are neither obvious differences in the methods of these 15 reviews compared to the remaining 23: in both sets less than 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).

In respect of the theoretical orientation, these 15 reviews show the same distribution as the other 23 reviews: 6/15 reviews focus on comparisons between behavioral, educational and other interventions (affective, complex, or other), 6/15 reviews address various interventions. 2/15 reviews address other combinations and 1/15 review technical solutions.

The only difference between the two sets of reviews is the number of reviews on technical solutions: 1/15 reviews compared to 5/23. In both sets of reviews 14 reviews were published between 2000 and 2005.

We must conclude that the characteristics of the two sets of reviews scarcely differed. The 15 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.

#### *Relatively effective adherence interventions*

There are 23 reviewers who found significant differences between the interventions and who made recommendations on particular types of adherence interventions.

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 - was not investigated in isolation.

Table 5.1 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 [63] and partner-focused strategies [73]. In addition, reviewers – already mentioned in Table 4 - also found some evidence for structural interventions, for example worksite care or community services [70,73,86]. We will now dwell in more detail on the theoretical principles underlying these adherence interventions.

We must acknowledge 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.



## 5.2 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. The underlying theoretical perspective of such interventions may be the bio-medical perspective, according to the theoretical analyses of Leventhal et al. [88]. Characteristic of the bio-medical model are 'technical solutions' for patients' adherence problems. In this model, the medical experts seek solutions for patients' problems. Patients need their expertise; they ask for help or advice.

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 [89]. 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 [88].

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 [26].

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 [29].

Although the quest for technical solutions is as old as mankind itself, we must confirm that as yet sound theoretical explanations for the effectiveness of simplification are lacking. The bio-medical model does not 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.

## 5.3 Behavioral theories

According to our findings, interventions based on incentives and reminders can be successful in improving patients' adherence. They represent in fact the basic 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 [88].

Over time, the behavioral approach has 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 [90].

Our findings of relatively successful adherence interventions fit in the behavior perspective. Behavioral adherence interventions focus directly on patients' non-adherence behavior. 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. Reminders and incentives thus reflect the powerful original principles of behavior theory. Our findings show that reminders are successful in improving appointment keeping and as such, sending reminders may be considered to be one of the easiest adherence interventions. It should be noted however, that patients' actual medication taking behavior seems less amenable to reminders. This remains a question for future research.

#### **5.4 Educational perspectives**

Patient education appeared to be relatively successful in five reviews. According to Brown, 'Educational interventions are defined as any intervention given with the intent of improving the person's ability to manage his/her disease, whether it be in the cognitive, psychomotor or affective domains' [58]. To make the meaning of 'education' more complicated, we also noticed that 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 [71]. Thus the concept of patient education is a complex one and does not solely refer to cognitive or didactic theoretical models.

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).

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. We will give a short characterization of each of these three theoretical mainstreams, which were originally distinguished by Leventhal et al. in their theoretical analyses [88].

##### *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. 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 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 [91,92]. 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) [88].

We must conclude that as yet it is unknown whether these three theoretical mainstreams are equally powerful or powerless in improving adherence. It should be noted that each of these theories seems to be plausible for explaining adherence behavior; however, interventions derived from these theories are not unequivocally effective. We must conclude that there appears to be a knowledge gap between, on the one hand, explaining adherence behavior, and on the other hand, improving adherence behavior.

Our results so far indicate some obvious findings concerning the theoretical perspectives underlying adherence interventions:

- firstly, there are effective adherence interventions – technical solutions - without a clear theoretical explanation of the operating mechanisms;
- secondly, there are effective adherence interventions – incentives and reminders – which clearly stem from the behavior theory;
- 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 [93].

On the basis of this study we formulated the following six propositions as tentative conclusions. These were presented for discussion to a selected forum of international adherence experts (see Annexes 7 and 8). Their recommendations and final conclusions are reported in Chapter 6.

## 5.5 Six tentative propositions

**1. Current adherence theories are more successful in explaining than in improving adherence: theory development should focus on improving adherence.**

Current adherence theories seem adequate to explain and understand adherence behavior. They seem to be less adequate for establishing effective adherence interventions. Just as in medical sciences, developments in diagnostics are superior to developments in therapy. A shift in focus is needed in adherence theories.

**2. Progress in adherence theories might be expected from conjoint efforts of medical, pharmaceutical, social and technical scientists.**

The importance of technical solutions in improving patient adherence points to new directions in theory development. Principles of technical sciences, for example from human engineering or ergonomics, could supplement the theories from medical and social sciences.

**3. To improve adherence, changing the situation seems more promising than changing the patient.**

The results indicate that practical and technical solutions and environmental adaptations are promising measures for improving adherence. Adherence should be considered in relation to a patient's environment. The starting point should be: 'what makes it easier for patients to adhere'?

**4. Adherence interventions should be limited solely to non-adherent patients.**

Interventions should be reserved for patients who need it. Until now, most adherence interventions have involved both adherent and non-adherent patients, leading to confusing and often contradictory findings. About two thirds of patients are spontaneously adherent. To them interventions are a waste of time and money and perhaps affect their autonomy. Identifying non-adherent patients is crucial. A first indicator is failing clinical progress. A second indicator lies in doctor-patient communication. Non-adherence should be discussed frankly and without blame.

**5. Patient groups should (help to) develop adherence interventions.**

Most adherence interventions have been developed by health care providers. Although research has focused on patients' reasons for non-adherence, patients have seldom been asked what they need to facilitate adherence. The time has come to consult patient groups about their needs and their wishes in relation to adherence.

**6. The main priority: simple interventions workable in (busy) clinical practice.**

Adherence interventions are growing increasingly complex. As a consequence they become less workable in full-day (busy) clinical practice. Most interventions require extra staff, often enabled by research funding. Other solutions are needed in clinical practice.

## 6 Recommendations and conclusions from expert forum

### 6.1 International expert forum

This final Chapter reports the recommendations and conclusions of international adherence experts. For that, the six propositions were discussed by an expert forum. The discussion was conducted via a private closed-circuit website. The main questions to the members of this forum were:

- a. Do you agree or disagree with the six propositions, and why?
- b. Which of the six subjects have the highest priority for future research and development? To that end, the members were asked to prioritize the propositions from number one (highest priority) to number six.

The summarized discussion has been authorized by all the members of the expert forum (see below). The results are reported in sections 6.2 to 6.8 and section 6.9 ends with an overall conclusion of this meta-review.

#### Members of the international expert forum

Barbui, C.	Roter, D.L.
Bender, B.G.	Schroeder, K.
Byrne, N.	Takiya, L.N.
Connor, J.	Van Dam, H.A.
Devine, E.C.	Van der Wal, M.H.L.
DiMatteo, M.R.	Van Eijken, M.
Giuffrida, A.	Vergouwen, A.C.M.
Haskard, K.	Vermeire, E.
Haynes, R.B.	Wild, M.
Iskedjian, M.	Yildiz, A.
Merinder, L.B.	

### 6.2 Theory development

**Proposition:** *Current adherence theories are more successful in explaining than in improving adherence: theory development should focus on improving adherence*

*Agree 5      Partly agree 4      Disagree 8      Other remarks 3      Total 20*

#### Weak explaining power of current theories

Many experts (n=8) disagree with the first part of the conclusion, that 'current theories seem adequate to explain adherence'. They notice that as yet there is hardly a sound theoretical basis for explaining adherence behavior, and that adherence theories hardly explain the variance in adherence (n=5). We don't see 'great strides forward in this area'.

Many experts (n=14) agree that most of current adherence interventions are not very successful in improving adherence. There are a number of theories and constructs (n=9) that have furthered our understanding of for example the cognitive processes underlying (non-)adherence. The many theories however, have not led to efficacious standard interventions improving adherence and the theories do not necessarily translate directly

into effective clinical strategies (n=5). Many theories focus on cognitive processes, but do not focus on barriers. Besides, theoretical frameworks have led to complex and costly interventions, not usable for wide distribution.

Non-adherence is a complex phenomenon (n=6) and it is notoriously difficult to change health behavior. Non-adherence may have many different causes. The factors and barriers vary between patient(groups) in different situations and there are many differences at individual level (n=7). Besides, many forms of non-adherence exist. There is for example a significant distinction between intentional adherence and non-intentional adherence. This distinction is not even considered in most theories. Different forms of non-adherence require corresponding situation-specific interventions and an individually tailored approach. Perhaps, multiple situation-specific theories are needed.

Theories are needed to understand the non-adherence phenomenon (n=7) and interventions should be based on findings from theories explaining adherence. Two experts argue that 'intervention'-theories are needed. But, there is a danger in re-focussing research efforts on purely intervention based theory, without in the first instance fully understanding the primary problem. There should be a two-way interaction between the development of theories and effective interventions.

### **Recommendations for theory development**

Better theories and better interventions are needed. Some of the experts gave the following recommendations with respect to (a shift in) future theory development. The following four items were mentioned by more than one expert. Future theory development should focus on:

- Different groups/forms of non-adherence (n=4)
- Physician-patient relation and communication (n=4)
- The individual's specific adherence problems and beliefs (n=3)
- The patients' perspective (n=3)

A more fundamental shift in focus is needed, according to three experts. Non-adherence should not be conceptualized as analogous to a pathology within the patient, and therefore needing to be 'cured'. Adherence is still being viewed from the providers' perspective and not the patients' ones. What do they want from health care and treatment and how well does professional care respond to this patients' perspective? To what extent does professional care really support and empower patients to find their way in health care, in self-care and in life? The focus would be better on the patients' side.

Three additional items for future theory development are: the development of adherence-facilitating clinical systems, for example to follow-up the drop-outs; improvement of doctors' prescribing behavior; and, efforts to fit theory to inexpensive (simple) interventions.

Finally, better studies are needed as well. Investigators should make use of standardized definitions of adherence and reliable measurement instruments, one should conduct more multidisciplinary studies and well conducted qualitative studies for a better understanding of adherence.

### 6.3 Multidisciplinary approach

**Proposition:** *Progress in adherence theories is to be expected from conjoint efforts of medical, pharmaceutical, social and technical scientists.*

*Agree 11      Partly agree 5      Disagree 1      Other remarks 0      Total 17*

#### **A multidisciplinary approach is vital**

A multidisciplinary approach is recommended by the majority of experts (n=15). A multidisciplinary approach of this problem is vital and is definitely the way forward.

Technology plays a large role in improving adherence.

Technical engineering could start by designing simpler and more effective treatments with fewer behavioral demands and fewer adverse effects. Human engineering and ergonomics might provide manufacturers with guidance concerning dosing, packaging and scheduling treatments. Technical solutions or innovations may provide passive, universal interventions that remove barriers for all (n=5). In addition, new technologies can support health care providers to monitor (non-)adherence and provide opportunities to discuss it with the patient. However, technical solutions alone are unlikely to be sufficient to assure adherence.

#### **Technology is just one part of the puzzle**

Nearly all experts argue that technical solutions are 'just one part of the puzzle'.

Psychosocial issues must be addressed as well. The main hurdles to adherence remain behavioral and humanistic in nature. Many more factors are involved in adherence: health care providers, systems of care, treatment modalities, social environment and so on.

Asking about adherence in a non-threatening manner and monitoring it should be universally adopted and reflects good health care. Adherence can be improved by discussing possible treatment choices with the patient and the logic behind them. It is more often the psychological variables which will ultimately determine lasting change.

Technical solutions may differ between clinical areas (n=4). In mental health care, the emphasis is on psychotherapeutic strategies which have shown at least some effect in improving adherence. Screening and monitoring adherence is needed. Individual assessment of reasons for non-adherence and application of motivational strategies should be priorities (in mental health care). Special attention should also be given to other patient groups, for example patients at high risk of non-adherence or vulnerable elderly people. In some clinical areas - for example type 2 diabetes care - biotechnical solutions are not immediately at hand. The emphasis is on the motivational and personal side of persons living with (such) health problems to support and empower them.

In a multidisciplinary approach, the link between the various disciplines can be understood as follows, according to one of the experts: a) medicine and pharmacy research and development identify new treatments; b) social science theories identify barriers to use the new treatments (i.e. explain non-adherence); and c) technical sciences (e.g. ergonomics, human engineering) are important tools to remove such barriers and improve use of and adherence to the new treatments.

Finally, as a relativation, one of the experts remarks that research on the treatment of sleep apnoea tells that technical apparatus variables and treatment side effects fail to explain a significant degree of variance in levels of adherent use. Those previous research findings should not be ignored in focussing on technical solutions.

## 6.4 Changing the situation

**Proposition:** *To improve adherence, changing the situation is more promising than changing the patient.*

*Agree 4      Partly agree 12      Disagree 2      Other remarks 0      Total 18*

### **Both are needed: changing the environment *and* the patient**

Some experts argue that it may be a bit too early to say that changing the situation is more promising than changing the patient (n=3). It is as yet unknown and evidence hardly exists. So far, neither (interventions) are doing very well.

According to nearly all experts, both are needed, changing environmental factors as well as the patients. Changing the situation is part of the non-adherence issue and can help patients to adhere. Of course, patients (and health care providers) will change when practical and technical solutions are used. Technology has much to offer regarding the manipulation of the environment and other treatment factors. Reducing technical and environmental barriers to adherence is important, but some patients need additional measures. Psychological variables, however, have been shown to be of at least equal importance in adherent behavior. Non-adherence is not always caused by technical or environmental variables. Basic knowledge and motivation is needed to make changes in life. Certainly, there is a place for behavioral and educational interventions.

### **Population or individual level**

Technical solutions apply more universally whereas psychological factors are more individual and require individual assessment and targeting. At population level, characteristics of the health care system may affect adherence (the way clinicians are trained, packaging or dosage regimen, costs). These causes need to be approached at system level. At an individual level contributing causes vary between groups and individuals. We need to distinguish patterns or types of non-adherence to chose tailored individual interventions (n=5). For some patients, non-adherence is a rational choice, some patients may benefit from removing (situational) barriers and others need to be educated.

### **Providers should change**

A number of experts address the provider. From the patients' point of view, changing the situation may need to include changing the prescribers' behavior. Prescribers should discuss (non-)adherence more openly with their patients and ask patients about adherence routinely.

Changing the situation also includes considering changing treatment guidelines, because it may be more realistic to adjust treatment to the patient than to adjust the patient to the treatment.

### **What makes it easier for patients to adhere?**

'What makes it easier for patients' is a worthy focus (n=4) and is a good starting point and we should always start with this question. The health care provider together with the patient should look at a solution that is feasible for the patient. Individual needs and difficulties of the patient should be identified. Whenever appropriate, simple solutions should be rendered to make life easier for the patient. However, making it easier - on its own - is unlikely to be sufficient to assure adherence.



## 6.5 Focus on non-adherent patients

**Proposition:** *Adherence interventions should be limited solely to non-adherent patients.*

Agree 2      Partly agree 6      Disagree 10      Other remarks 0      Total 18

### **If it were possible to identify non-adherent patients...**

Many experts agree that non-adherent patients could benefit most of interventions, but nonetheless most of them (n=10) disagree with this fourth proposition. The main point here is the identification of non-adherent patients. Of course, it is more efficient and affordable to focus on patients who need help. Preferably, (complex) interventions should be limited to those who need them, provided that those people can be identified (n=5). According to nearly all experts, it appears to be difficult or often impossible to identify the non-adherent patients. Providers cannot reliably distinguish adherent from non-adherent patients, although they insist that they can. Failed clinical progress is not a reliable indicator, because of the weak correlation between adherence and outcome, and we still hardly know how much adherence is enough.

### **Adherence changes with time**

According to many experts (n=7) there is not a clear distinction between adherent and non-adherent patients: it is a continuum. Besides, adherence fluctuates and changes over time: adherent patients may become non-adherent ones (n=4). We must also focus on the prevention of non-adherence (n=4). In addition, the aim of psycho-educational interventions is not only to improve adherence but has other aims as well, for example to increase patients' knowledge about disease and treatment. In this regard, all patients could benefit from interventions.

A distinction can be made between interventions which should be universally applied to all (for example technical solutions) and other individually tailored interventions. Different strategies may be applied, for example for short term or long term regimens. For long term regimens, it remains important to put adherence permanently on the agenda in the doctor-patient communication, even if the patient seems to be adherent. Adherent patients should not be ignored.

### **Doctor-patient communication is crucial**

Many experts (n=8) point to the importance of the doctor-patient communication in adherence. Communication is an essential piece of this puzzle. Over and over again, the quality of the staff-patient relationship appears to be central to adherent behavior. Respect for the patient and collaborative treatment goals are services which have no financial costs attached and should anyway be part of basic clinical practice. The communication requires patients to be comfortable discussing with their providers the difficulties they may be having with a regimen, so that the regimens can be modified as needed (n=4). The clinicians' awareness and practice of monitoring adherence should be improved. Non-adherence should be monitored in everyday practice.

## 6.6 Patient involvement

**Proposition:** *Patient groups should (help to) develop adherence interventions.*

Agree 16      Partly agree 0      Disagree 0      Other remarks 0      Total 16

### **Consensus about a patient-centred approach**

The experts (n=16) agree unanimously that focusing on patients is crucial to improve adherence. The time has come to consult patient groups about their needs and their wishes in relation to adherence. Patient(groups) should help develop adherence interventions. For too long, we have tried to squeeze clinical populations into our existing models. A patient-centred approach will surely lead to environmentally valid theories. However, investigating the reasons of patients' perceived needs and wishes may partly be based on false ideas and beliefs about disease and treatment. We should also inquire into patients' reasons for non-adherence and the barriers to adherence.

Patients may differ in their needs and wishes. Certain interventions developed by certain patient groups may only be effective in a certain population. Many different patient populations should be consulted and should be represented: patients from different backgrounds, age, gender and other socio-demographic characteristics. Experienced patients can also help health care providers with their own 'tips and tricks' that helped them to adhere.

### **What patients want**

There is much we already know about what patients want. Patients who forget want simplified regimens and a reminder system. Patients who get side effects want them to disappear. Patients who think the medication won't help, don't want to take them after all. Fortunately, the use of focus groups and other techniques seems quite established nowadays. Increasingly, reasons for non-adherence are being discussed, but adherence interventions are seldom tailored to the patients' wishes.

### **The professionals' experiences**

Perhaps the best way to proceed concerns the adherence-experiences of the professionals themselves. Most of them have experienced (adherence to) self-administered treatments. Perhaps we should require the treatment developers to take the treatment (or facsimile/placebo) themselves for a period of time. Similarly, those who have developed adherence interventions could try it on themselves or their family and friends, besides discussing it with a group of patients.

## **6.7 Simple interventions**

<b>Proposition:</b> <i>The main priority: simple interventions workable and feasible in (busy) clinical practice.</i>
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<i>Agree 12</i>	<i>Partly agree 5</i>	<i>Disagree 0</i>	<i>Other remarks 0</i>	<i>Total 17</i>
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### **Much agreement on simple interventions**

Simple and down-to-earth interventions are badly needed, according to the majority of experts (n=12). Efficient and cost-effective interventions are crucial to success. It is important to assess the cost-effectiveness of interventions in the long term, when patients are no longer part of a research study. The growing complexity of interventions reflects a lack of understanding of adherence.

The interventions should not only be simple for the professional but for the patient as well. There is some reason for optimism. For example, a simple intervention as meeting the outpatient staff before hospital discharge may improve adherence. Technical approaches should be used wherever possible, for example telephone reminders. They may not be the biggest contributors but they may reduce clinical load over time.

### **Assessment of adherence should be routine**

Many experts (n=9) argue that usual care should be improved. Upskilling of clinicians is a simple and promising means to improve adherence. Good communication and collaboration is free, fits within daily clinical practice and should already be part of any clinicians' basic practice. To address adherence must be a routine part of the visit, just like taking blood pressure. Improvements of adherence is not only part of the physicians' work, but should be the work of a multidisciplinary team in which nurses could play an important role, for example by chronic disease management.

There will always be patients who require more intensive (and therefore more expensive) guidance and support from the health care team. Therefore, it is in particular important to identify suboptimal adherence in the earliest stages. We need more predictors of non-adherence and for example screening tools to identify groups at risk for non-adherence. This continues to be a big challenge in clinical practice.

### **Increasing complex medical regimen**

The problem is that the regimens patients have to follow are often becoming increasingly complex, for example because of co-morbidity, especially in chronically ill elderly patients. In such cases simple and short interventions hardly exist and more complex interventions require time and money. However, with the improvement of adherence, unnecessary re-admissions can be prevented and quality of life can be improved.

## **6.8 Priorities**

Finally, we give the rank order of priorities, as assigned by the members of the expert forum.

- |                                      |   |
|--------------------------------------|---|
| 1. <i>Future interventions:</i>      | Explore simple interventions workable and feasible in (busy) clinical practice.                         |
| 2. <i>Future theory development:</i> | Explore new directions by conjoint knowledge of medical, pharmaceutical, social and technical sciences. |
| 2. <i>Future research:</i>           | Explore the usefulness of patient participation in the development of (new) interventions.              |
| 2. <i>Future research:</i>           | Identify non-adherent patients and apply interventions to this group specifically.                      |
| 3. <i>Future theory development:</i> | Focus on improving adherence.   |
| 4. <i>Future research:</i>           | Explore interventions directed at changing situational factors in adherence.                            |

There is not a definite (100%) consensus about the priorities for future research and development, because each of the statements received a number of priority scores above average (1 to 3) as well as some priority scores below average (4 to 6) (See appendix 7). Nevertheless, a 'priority pattern' can be seen.

Priority above average is assigned (by 76% of the experts) to the development of simple interventions, workable and feasible in busy clinical practice.

Priority below average is assigned to two propositions: firstly to research on interventions

directed at changing situational factors in adherence (by 71% of the experts), and secondly, to the proposition that future theory development should focus on improving adherence (by 65% of the experts). The other three propositions approximate circle around average priority.

## **6.9 Overall conclusions**

The outcome of the forum discussion indicates that the International Expert Forum on Patient Adherence chose the development of simple interventions as the most promising way to take in fostering patient adherence, preferably within a multidisciplinary setting of medical, pharmaceutical, social and technical science and, not in the least, by incorporating patients' perspectives. The theoretical underpinning of this perspective is not straightforward; within this line of research and practice biomedical models, behavioural theory as well as educational perspectives come to the fore. The priorities do indicate that most success is expected to be gained by listening to what the patients themselves consider worthwhile interventions. After all, the meaning of 'simple' in relation to adherence interventions can only be deciphered by listening to the patient. Patients are the experts when trying to disentangle what constitutes a simple intervention, e.g. as being not too intrusive or invasive nor time-consuming, costly or incorporating many uncomfortable side effects. Disclosing these patients' perspectives does require to make an open discussion of patients' expectations, needs and experiences in taking medication a standard procedure within medical practice and to pay attention to what patients might help to become and remain adherent. This is a challenge for every health professional.

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**Literature searches**



## Search strategy COCHRANE DATABASE dd. 1-2-05

#1 compliance:ti (1990 to current date): 864 titles

#2 adherence:ti (1990 to current date): 396 titles

#3#1 OR #2: 1255 titles

#4 screening:ti OR (guideline:ti NEXT adherence:ti) OR (reproductive:ti NEXT control:ti) OR prevention:ti (1990 to current date): 10266 titles

#5#3 NOT #4: 1178 titles

Excluded: 1067 in Cochrane Central Register of Controlled Trials

Included:

5 titles in Cochrane Database of Systematic Reviews – Complete Reviews

16 titles in Database of Abstracts of Reviews of effects – Abstracts of quality assessed systematic reviews

3 titles in Database of Abstracts of Reviews of effects – Other reviews

A total of 24 review titles included in the original literature list.

## Search strategy EMBASE dd. 02-03-05

No.	Records	Request
1	26430	"patient-compliance"/ all subheadings
2	85283	explode "practice-guideline"/ all subheadings
3	37089	explode "mass-screening"/ all subheadings
4	208039	explode "agents-acting-on-the-genital-system"/ all subheadings
5	255841	explode "prevention"/ all subheadings
6	546750	#2 or #3 or #4 or #5
7	<b>20286</b>	<b>#1 not #6 = Compliance</b>
21	569340	"review"/ all subheadings
22	3060	"systematic-review"/ all subheadings
23	20324	"meta-analysis"/ all subheadings
24	582585	#21 or #22 or #23
25	550716	review in dt
26	0	meta analysis in dt
27	0	review in pt
28	0	meta analysis in pt
29	<b>582642</b>	<b>#24 or #25 := Reviews</b>
30	<b>3357</b>	<b>#7 and #29 (Combination of Compliance &amp; Reviews)</b>
<b>Refinements 1:</b>		
31	194697	"drug-efficacy"/ all subheadings
32	50069	explode "drug-metabolism"/ all subheadings
33	30531	"drug-potency"/ all subheadings
34	20655	"drug-potential"/ all subheadings
35	4211	"drug-intoxication"/ all subheadings
36	<b>280888</b>	<b>#31 or #32 or #33 or #34 or #35 (Excluded aspects)</b>
37	<b>2485</b>	<b>#30 not #36 (Combination Compliance &amp; Reviews &amp; excluded aspects)</b>

### Refinements 2

- 38 22294 #22 or #23 (Restricted reviews: 'systematic review' en 'meta-analysis')
- 39 345 #7 and #38 (Compliance and (restricted) reviews).
- 40 205 #39 not #36 (Idem, and excluded aspects)
- 41 691492 patient

### Refinements 3

- 42 50371 compliance
- 43 3867 patient compliance in dem (Compliance & 'patient compliance' as major keyword)
- 44 452 #29 and #43 (Compliance & Reviews)

**A total of 452 titles included in the original literaturelist.**

### Search strategy PSYCHINFO dd. 1-2-05

#### Search History

#4 ("Compliance-" in MJ,MN) or ("Treatment-Compliance" in MJ,MN)(5009 records)

#5 "Treatment-Dropouts" in MJ,MN(880 records)

#6 ("Treatment-Dropouts" in MJ,MN) or (("Compliance-" in MJ,MN) or ("Treatment-Compliance" in MJ,MN))(5751 records)

#8 ("Literature-Review" in MJ,MN) or ("Meta-Analysis" in MJ,MN)(11202 records)

#9 REVIEW in DT(5323 records)

#10 (REVIEW in DT) or (("Literature-Review" in MJ,MN) or ("Meta-Analysis" in MJ,MN))(16520 records)

#11 ((REVIEW in DT) or (("Literature-Review" in MJ,MN) or ("Meta-Analysis" in MJ,MN))) and (("Treatment-Dropouts" in MJ,MN) or (("Compliance-" in MJ,MN) or ("Treatment-Compliance" in MJ,MN)))(47 records)

**A total of 47 reviews included in the original literature list.**

## Search strategy PUBMED dd. 1-2-05

□ Search	Most Recent Queries	Time	Result
#2	Search "Patient Compliance"[MeSH] Field: All Fields, Limits: Publication Date from 1990/01/01	04:26:25	<u>17638</u>
#3	Search "Guideline Adherence"[MeSH] OR "Mass Screening"[MeSH] OR "Reproductive Control Agents"[MeSH] OR "Primary Prevention"[MeSH] Limits: Publication Date from 1990/01/01	04:27:42	<u>103936</u>
#4	Search #2 NOT #3 Limits: Publication Date from 1990/01/01 ( = Compliance)	04:28:27	<u>16323</u>
#9	Search "Review Literature"[MeSH] OR "Meta-Analysis"[MeSH] Limits: Publication Date from 1990/01/01	04:41:27	<u>7301</u>
#10	Search review literature[pt] OR meta-analysis[pt] Limits: Publication Date from 1990/01/01 (= Meta-analysis[pt] )	04:43:19	<u>9867</u>
#15	Search meta-analysis[pt] Limits: Publication Date from 1990/01/01 ( = meta-analysis[pt] )	04:47:55	<u>9867</u>
#16	Search review[pt] Limits: Publication Date from 1990/01/01	04:48:07	<u>814527</u>
#17	Search literature AND (review OR reviews) Limits: Publication Date from 1990/01/01	04:48:35	<u>95046</u>
#18	Search #16 AND #17 Limits: Publication Date from 1990/01/01	04:48:58	<u>70057</u>
#19	Search #9 OR #15 OR #18 Limits: Publication Date from 1990/01/01 ( = Reviews).	04:50:27	<u>85548</u>
#20	Search #4 AND #19 Limits: Publication Date from 1990/01/01	06:55:18	<u>405</u>
<b>A total of 405 reviews included in the original literature list</b>			

Results of literature searches: 928 reviews.

After removing duplicates a total of 918 reviews in the original literature list.



**Score form inclusion criteria**





## Checklist for inclusion and exclusion of reviews

Author and year of publication .....

Subject of the review	yes	no	unclear
Adherence to medical treatment prescribed by health professional			
Research question Effectiveness of interventions/measures to increase adherence			
Literature search Electronic literature searches			
Primary studies In- and exclusion criteria are applied to primary studies			
Review method Meta analysis			
Results of review Reported in quantitative and tabulated way			

### Final judgement

0 Inclusion

0 Exclusion

0 Unclear

### Main reason for exclusion

*Focus of the review on:*

0 prevention

0 (new) medication/treatment effects

0 guideline adherence

0 on outcome (without adherence)

0 on factors related to adherence

0 on magnitude of adherence

0 other:.....

*Methods of review*

0 descriptive review

0 qualitative results

0..literature searches unclear

0 inclusion criteria studies unclear

0 other:.....



### **Tabulated overview of included reviews:**

- general review characteristics
- interventions
- review results
- reviewers' conclusions
- reviewers' recommendations



First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Bender B. et al., 2003 Asthma Search 1992-2003 16 studies 3606 patients		Review	1) Educational 2) Behavioral	1) Improvements in 9/16 studies 2) Self reported adherence was often not accompanied by treatment success	1) There is little concurrence in reports of adherence interventions 2) Many interventions involved a significant amount of professional time yet few were very effective	Research into innovative interventions, that are brief easily implemented and can be tailored to individual patients and diverse clinical settings	Inclusion of hard-to-reach and of poor patients, use valid measures of adherence at intervals, sufficient to establish enduring benefit	The need for methodological sound studies of innovative approaches to adherence promotion is evident
Brown SA, 1990 Diabetes (I and II) Search 1961-1989 82 studies 5348 patients		Meta	Various interventions	1) Knowledge effects: ES range 0.49-1.05 2) Self care effects: ES range 0.17-0.57 3) Metabolic control: ES range 0.16-0.41 4) Psychological outcomes ES 0.27	1) This meta-analysis lends support to the effectiveness of diabetes patient education in improving patient outcomes 2) It is unknown what types of educational strategies are most effective	Ensure that more diabetes patients have access to patient education programs	1) Description of study sample and sampling procedure 2) Description of interventions	Details of most studies related to how the research was conducted and little attention was given to describing the interventions
Buring SM et al., 1999 Peptic ulcer (H.pylori) Search 1990-1996 63 studies 5996 patients	63 RCT	Meta	The number of daily doses	1) The more dd's, the more dropouts 2) ADR-documentation, more dropouts 3) Symptomatic relief, less dropouts	High number of doses per day results in higher discontinuation	An ideal regimen would have one or two drugs and fewer than three doses/day	Future trials should include: minimum compliance standards; adverse effect diaries or interviews; intent-to-treat analyses	None
Burke LE et al., 1997 Cardiovascular (+ risks) Search 1977-1997 46 studies 29,485 patients	46 RCT	Review	Various interventions	13 strategies were successful, among them: behavioral skill training self-monitoring telephone/mail contact self-efficacy enhancement external cognitive aids etc.	1) This review reflects the progress made over two decades in compliance measurement and research 2) The majority of the interventions have not been tested in controlled studies for comparative efficacy	1) One of the challenges is to reduce the gap between compliance in clinical trials (not ideal) and compliance in clinical practice (even lower) 2) Focus interventions on the subgroups identified as non-adherent	1) Test comparative efficacy of successful strategies 2) Focus on subgroups of non-adherent patients	Despite the progress made in compliance research, compliance rates have remained nearly unchanged during the last 20 years

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Claxton AJ et al., 2001 Various diseases Search 1986-2000 76 studies	76 RCT MEMS (elec.monit.)	Review	Number and timing of doses	1 dose, compliance = 79% 2 doses, compliance = 69% 3 doses, compliance = 65% 4 doses, compliance = 51%	1) The number of doses per day is inversely related to compliance 2) The mean dose-taking compliance rate ranged from 70% to 80% in all but respiratory disease, indicating the similarity of compliance rates across therapeutic areas	1) Simpler, less frequent dd's, better compliance 2) EM-devices could be used in clinical practice to evaluate the reason for lack of expected treatment effect	1) Further recognition of the influence of medication compliance on health outcomes will enhance research in this area 2) Further research is needed about dose timing	Monitoring compliance with EM-device has not been demonstrated to influence compliance; such monitoring is not sufficient to change behavior
Connor J. et. al., 2004 Various diseases Search 1966-2003 15 studies 3.561 patients	15 RCT	Review	1) Packaging (unit-of-use packaging) 2) Fixed-dose combination pills	1) Improvements in 3/15 studies 2) Improved adherence in 7/13 studies	1) Fixed-dose combination pills and units-of-use packaging are likely to improve adherence 2) Uncertainty remains about the size of these benefits	1) The paucity of reliable evidence about effective strategies for improving adherence is extraordinary given the investment in assessing the efficacy of separate medications and the number of individuals taking multiple medications 2) Development and evaluation of fixed-dose combination products for developing countries	Improve methodological quality: larger samples; follow-up at least 6 months; blinding subjects and dealing with subject losses	There seems to be little incentive for companies to invest in combinations of off-patent products that might compete with on-patient monotherapy
Devine EC, 1996 Asthma Search 1972-1993 31 studies 1.860 patients	18 RCT	Meta	Psycho-educational care	1) Improved adherence ES is =.78 2) Eight of nine outcomes improved: ES .35	Both education and relaxation-based behavioral interventions have been shown to improve important clinical outcomes in adults with asthma	The provision of psychoeducational care is well justified by the existing research	Methodological weaknesses should be rectified in future research (report duration of the intervention; details and severity of the lung disease; random assignment; placebo-type control treatment	Placebo-control is needed to test the relative effect of specific treatments over the generic effect of the psychosocial support from an interested caregiver

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Devine EC et al., 1995 Hypertension Search 1965-1993 88 studies 6.581 patients	51 RCT	Meta	psycho-educational care	1) Improved knowledge ES= 1.03 2) Medication compliance ES=.74 3) Appointment keeping ES=.47	1) Significant large effects were obtained on: knowledge; medication compliance; compliance with appointments 2) Effects on weight are unknown (due to methodological weaknesses)	Education, self monitoring of blood pressure and mobilizing psychosocial supports should be considered appropriate nursing interventions for outpatient adults with hypertension	Avoid three current methodological weaknesses: underreporting (sample, duration, e.g.); no multiple blood pressure measures at pretest; few studies compared different types of psychoeducational care	Effects on blood pressure were significantly smaller in studies with multiple pretest measures of blood pressure, (because) blood pressure tends to decrease over time when it is measured on multiple occasions
DiMatteo MR, 2004 Various diseases Search 1948-2001 122 studies 12.010 patients		Meta	Social support	1) Practical social support: ES=.65 2) Emotional social support: ES .30 3) Unidimensional social support: ES=.43 (other relations with adherence set aside)	1) There is solid quantitative evidence that social support has substantial effects on patient adherence 2) Practical social support bears the highest correlation with adherence	1) Practical support is a potentially important target for interventions 2) In clinical settings it is important to assess the type and quality of patients' relationships to assist them to receive most benefit from treatment	1) More systematic empirical study is needed, including multidimensional longitudinal research 2) Comparisons among various types of acute and chronic conditions to determine exactly how social support works to affect adherence	1) Studies using self report of adherence yield higher correlations (r=.35) than other measures (r=.20) 2) At the aggregate level there is no evidence that the mean effect is a result of the use of self-reports
Dodds F et al., 2000 Psychotic disorder Search 1984-1999 8 studies 543 patients	8 RCT follow-up 6 m	Review	Various interventions	1) Improved compliance in 3/8 studies	1) Compliance can be improved by certain, sometimes complex, interventions 2) Effective interventions included: individualized behaviour tailoring regimes and compliance therapy	The evidence supports using a combination of daily living activities and medication regimes combined as a behavioural reminder, incorporated as a joint activity and not treated as a separate entity	More larger (field) studies are needed	1) Further efforts are needed in developing effective interventions 2) The implicit assumption that knowledge improves compliance is unfounded

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Dolder Chr et al., 2003 Schizophrenia Search 1980-2001 21 studies 2394 patients	16 RCT	Review	Educational Behavioral Affective Combinations	1) Improvements in 15 of 23 interventions 2) Education effective: 1/4 studies 3) Behavioral int. effective: 2/2 studies 4) Affective int. effective: 4/5 studies 5) Combined int. effective: 8/12 studies	1) Education only is least successful 2) Combinations were more effective 3) Longer interventions are important, and alliance with the therapist	1) Monitor regularly patient's level of adherence 2) Detect risk factors for non-adherence 3) Implement strategies to address these factors 4) Appropriate therapy intensity and duration	1) Effective interventions are needed 2) Large samples (for subgroup analyses) 3) Use multiple measures of adherence 4) More RCT's and long(er) follow-up	1) The active components in multiple strategy interventions are difficult to isolate, 2) The use of multiple strategies may dilute what was originally effective in single strategy interventions
Giuffrida A et al., 1997 Various diseases Search 1966-1997 11 studies 2721 patients	11 RCT	Review	Financial incentives	1) Improved adherence in 10/11 studies 2) Financial incentives promoted compliance better than any alternative intervention	1) Financial incentives can significantly reduce non-compliance 2) Incentives can be cost-effective, particularly for treatment of infectious disease	In areas of health care where important individual or external effects are associated with non-compliance, monetary incentives may be relatively cost effective (for example: infecting others; development of drug resistance strains)	RCT's outside USA needed (all studies from USA)	It is unknown whether cash or gifts are more effective, but cash payment would be expected to be more effective
Haynes RB et al., 2005 Various diseases Search 1967-2004 57 studies 10,010 patients	57 RCT 6 months follow-up 80% follow-up	Review	Various interventions a) for short term treatments b) for long-term treatments	1) Short term treatment: 4/9 interventions effects on adherence and outcome 2) Long-term treatment: 26 of 58 interventions effects on adherence, and 18/58 interventions effects on outcomes	1) Improving short term adherence is relatively successful with a variety of simple interventions 2) Current methods of improving adherence for chronic health problems are mostly complex and not very effective 3) Efforts to improve adherence must be maintained for as long as the treatment is needed: low adherence cannot be 'cured'	Perhaps the most important simple intervention, given its simplicity and effectiveness, is recalling patients who missed appointments, making every effort to keep them in care	1) High priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long term medical disorders 2) Perhaps include patients in the development of new interventions	1) Investigators should join across clinical disciplines to tackle the problem. 2) Take into account patients' resistance to taking medicines 3) The common thread (to complex interventions) is more frequent interaction with patients with attention to adherence



First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Higgins N et al., 2004 Various diseases (older people) Search 1966-2002 7 studies 1030 patients	6 RCT	Review	1) Medication schedules 2) Education 3) Combinations	1) Improved adherence: 3/7 studies	1) There is no robust evidence supporting any one type of approach 2) Successful interventions are likely to be combinations 3) Significant effects tended to have small effects clinically 4) Single discrete interventions were disappointing	There is not yet any strong evidence to support the use of any one type of intervention to help improve adherence amongst older people	1) Methodological well-designed RCT's are needed 2) Sophisticated combinations of approaches tailored to a patient's individual needs	1) Problem: complex interventions contain multiple elements. It is therefore difficult to conclude what aspects are effective 2) None of the interventions tackled the issue that patients might actively choose not to take medication
Iskedjian M et al., 2002 Hypertension Search 1980-1998 8 studies 11,485 patients		Meta	1) One daily dosing 2) Two daily dosing 3) Multiple daily doses	1) One dd adherence = 91-93% 2) Two dd adherence = 87-91% 3) Multiple dd adherence = 83-86%	1) One dd is associated with higher rates of adherence than either two dd's or multiple dd's with antihypertensive medications 2) A simple one dd regimen alone may not result in adequate compliance	One way to establish clinical relevance of an intervention is by calculating the number needed to treat (NNT): to have one additional adherent patient, switch 12 patients from MMD to IDD	None	The medical consequences may be more grave for those patients failing to adhere to 1dd regimens, since missing one dose results in missing the total daily dose
Macharia WM et al., 1992 Various diseases Search 1966-1990 23 studies 5285 patients	23 RCT	Meta	1) Cuing (reminders) 2) Reducing barriers 3) Increasing motivation	1) Mailed reminders: OR 2.2 (1.7-2.9) 2) Telephone prompts: OR 2.9 (1.9-4.3) 3) Orientation statement: OR 2.9 (1.5-5.6) 4) Contracting with patients: OR 1.9 (1.0-3.5) 5) Prompts from physicians: OR 1.6 (1.4-2.0)	1) In clinic settings broken appointments can be reduced by mail, telephone, or physician reminders, orienting patients to the clinic; or contracting with patients 2) Keeping appointments can be an accurate measure of patient compliance	1) The benefit of interventions is greatly influenced by the baseline rate of appointment keeping (NNT) 2) Whether an intervention is worthwhile also depends on the consequences of a missed appointment	1) Studies are needed on repeated prompts because a decay in effects may occur 2) Effectiveness of reminders for screening in the general population needs further study	The results cannot be safely extrapolated to self-administered treatments; the results concern supervised administration of care

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Merinder LB, 2000 Schizophrenia Search 1966-1997 19 studies 1718 patients	15 RCT	Review	Patient education	1) Improved knowledge: 6/11 studies 2) Improved compliance: 6/11 studies 3) Reduced relapse: 3/7 studies	1) Knowledge and compliance can be improved by educational intervention 2) No influence of the duration of interventions was found	1) Didactic formats influence knowledge more readily 2) Behavioural components are more efficacious in influencing compliance	1) Further methodologically homogeneous and better reported studies are needed 2) Better descriptions of interventions 3) Comparisons between different interventions (in duration, intensity and educational method)	1) Due to methodological limitations and the results are far from conclusive 2) Interventions seem to develop towards the use of a more didactic interactive format (negotiations of individual illness model)
Morrison A et.al., 2000 Hypertension Search 1965-1999 29 studies 12.835 patients	24 RCT	Meta	Various interventions	1) Worksite care: significant effects 2) Physician education: sign.effects 3) Electronic vial cap: sign.effects 4) Patient cards: sign.effects (tentative) 5) Calendar packaging: sign.effects (tentative) 6) Reminders mailed: insufficient evidence 7) Patient education: conflicting results 8) Patient counseling: inconclusive 9) Self monitoring: ineffective	Results for meeting goal diastolic blood pressure, when evaluated, were generally in accordance with those for adherence	P & T Committees should consider whether compliance programs incorporating effective interventions would benefit their patient populations	Many of the trials lacked blinding (patients and accessors) and this is a potential source of bias	1) In two trials, patient education reduced diastolic blood pressure, but did not improve adherence: 2) Perhaps patient education helps lower blood pressure by means independent of drug therapy

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Mullen PD et al., 1992 Cardiac Care Search 1971-1992 28 studies 4995 patients	Meta	Patient education	1) Exercise: effects: ES = 0.18 2) Diet: effects ES = 0.19 3) Smoking: effects not significant 4) Drug adherence: effects not significant (blood pressure: effects ES 0.51) (mortality: effects ES = 0.24)	1) Cardiac patient education programs have a measurable impact on blood pressure, mortality, exercise and diet 2) Type of communication channel did not influence outcome; 3) Applying five principles of education was associated with larger effects. 4) No differences were found for number of contacts or total contact hours	The use of educational principles is recommended: reinforce positive behavior; offer feedback (on progress); individualize educational program; facilitate behavior; relevance to the learner's interest and situation	Use of control groups is strongly advised	1) The results suggest that it is not the time spent 2) No difference between didactic vs behavioral, apparently because of relatively intensive affective interventions in the didactic group	
Newell SA et al., 1999 Cardiovascular disease Search 1985-1996 20 studies 4226 patients	Review	1) Patient focused strategies 2) Structural strategies 3) Physician focused strategies	1) Medication taking: effective 2/6 studies 2) Refill compliance: effective: 3/3 studies 3) Appointment keeping: effective 8/11 studies	1) Tentative recommendations for many patient focused and structural strategies 2) Tentative recommendations against physician focused strategies	The methodological quality of many trials were not optimal, prohibiting strong recommendations	Overcome methodological flaws of current studies: randomized controlled trials follow-up at least 6 months a no-intervention control group adequate sample sizes direct objective measure of compliance or multiple outcome measures	Despite the limitations we believe that this review represents one of the most rigorous that has been conducted of the recent literature	

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Newell SA et al., 2000 Cardiovascular disease Search 1985-1996 18 studies	18 RCT	Review	Various interventions	1) Diet: effective 5/15 studies 2) Smoking: effective 1/12 studies 3) Exercises: effective 6/9 studies 4) Weight-loss: effective 3/7 studies 5) Lifestyle: effective 1/4 studies 6) Screening blood pressure: effective 1/2 7) Stress management: effective 0/1 8) Relaxation adherence: effective 4/5	1) Strong recommendations were made for 3 out of 27 interventions: smoking: audiovisual material weight loss: compliance monitoring and feedback for weight loss 2) Patient focused strategies showed mixed results 3) Tentative recommendations for structural and partner focused strategies 4) Physician focused strategies were unanimously unsuccessful	The methodological quality of many trials were not optimal, prohibiting strong recommendations	Overcome methodological flaws of current studies: randomized controlled trials follow-up at least 6 months a no-intervention control group adequate sample sizes direct objective measure of compliance or multiple outcome measures	1) Despite the limitations we believe this review represents one of the most rigorous conducted of the recent literature 2) The low quality of studies is disappointing because similar criticisms have been raised before in previous reviews
Nosé M et al., 2003 Schizophrenia Search 1980-2003 24 studies 3578 patients	14 RCT	Meta	Educational strategies Psychotherapy Prompts Specific services Family interventions	1) Educational strategies: effects OR = 2.41 2) Psychotherapy: effects OR = 2.83 3) Prompts: effects OR = 1.87 4) Specific services: effects OR = 3.63 5) Family interventions: effects OR = 4.45	1) Overall odds ratio is 2.59 for dichotomous outcomes (95% CI 2.21-3.03) and a standardized mean difference of 0.36 for continuous outcomes 2) Thus, these interventions more than double the likelihood of adherence to psychotropic medications and to scheduled appointments 3) No intervention emerged as predictor of overall treatment effect 4) This does not imply that all interventions are equally effective	Community psychiatric services can potentially use effective clinical interventions, backed by scientific evidence, for reducing patient non-adherence	1) Experimental studies have to address the effectiveness of different strategies in large samples. 2) Long term follow-up is needed to assess long-term effects 3) Trials must adopt high (methodological) standards	Effects of interventions were greater in studies with a short follow-up period (OR 2.27, 95% CI 1.78-2.90) than those with a follow-up of 6 months or more (OR 1.70, 95% CI 1.04-2.78)

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Pampallona S et al., 2002 Depression Search 1990-1999 32 studies 12.454 patients	14 RCT	Review	Psychological treatment Patient education Family education Training physicians Training nurses Changing treatment Medication clinics	1) The studies did not give consistent indications of which interventions are effective 2) Even looking at contrasts, as we did, does not disentangle the effects of each component	1) By implementing several interventions at the same time, many studies could not provide evidence on the separate effects of the components 2) The question is whether all the components are needed in combination 3) The trend is that more interventions generally showed a higher adherence rate	Evidence suggests that adherence can be improved	1) Carefully designed clinical trials are needed to clarify the effects of single and combined interventions on adherence. 2) Such studies and the interventions should be feasible in busy clinical practice	none
Peterson AM et al., 2003 Hyperlipidemia Search 1966-2000 4 studies 3077 patients	4 RCT	Meta	Behavioral Educational Combination	1) Behavioral interventions: ES = 0.14 2) Educational interventions not single applied 3) Combined interventions: ES = 0.03	The interventions had little impact on drug adherence	1) Five (of seven) interventions consisted a change in drug type (from bile acid sequestrants to statins or niacin) 2) Given that statins are now regarded as first-line agents, it is difficult to generalize the findings of this study to current treatment regimens	More studies are needed to assess how to improve drug adherence in patients with hyperlipidemia	Traditional interventions to improve drug adherence in patients with hyperlipidemia have little impact

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Peterson AM et.al., 2003 Various diseases Search 1966-2000 61 studies 18,922 patients	61 RCT	Meta	Behavioral Educational Combination	1) behavioral interventions: ES = 0.07 2) educational interventions: ES = 0.11 3) combined interventions: ES = 0.08	1) There were no significant differences among behavioral interventions 2) There were no significant differences among educational interventions 3) Of combined interventions, mail reminders had the largest impact ES=0.38 followed by skill building ES=0.17, packaging ES=0.14 and dosing ES=0.12 4) The overall mean increase in medication adherence was 4-11%	For many decades we have searched for that one perfect solution to the problem, however, there does not seem to be any one intervention that robustly enhances adherence, perhaps because so many variables affect a patient's decision to take a drug	1) A standard definition and a standard measure of adherence are needed and a standard format for reporting data 2) More studies are needed between adherence and health outcome	1) Roter found an ES between 0.17-0.27, but she included also nonrandomized studies 2) Nonrandomized trials may have overestimated the true effects
Richter A et.al., 2003 Various diseases Search 1985-2002 62 studies		Review	Dose reduction	1) Dose reduction effective in 12/13 studies	1) Reducing the number of daily doses has frequently been shown to provide the patient with better symptom control 2) Overall improvements were seen in adherence, quality of life, patient satisfaction and costs	Where reducing the dose frequency is feasible, it may offer benefits for the patient in terms of health outcome and for the health care budget holder in terms of costs (some medications are not suited for reducing dose)	Persistence with medication in chronic diseases remains an area for future research	Probably the single most important action that health care providers can take to improve adherence is to select medications that permit the lowest daily prescribed dose frequency (citation Eisen et.al.1990)

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Roter DL et al., 1998 Various diseases Search 1977-1994 153 studies 57.528 patients	116 RCT	Meta	Educational Behavioral Affective Combinations Provider directed	1) Educational interventions ES = 0.23 (dir)* 2) Behavioral interventions ES = 0.17 (dir) 3) Affective interventions ES = 0.31 (dir) 4) Combined interventions ES=0.19-0.34 (dir) *) dir = direct measures of adherence	1) Significant effects for all the compliance indicators 2) Compliance interventions had a weak to moderate statistical effect 3) Smaller effects were evident for improved health outcomes 4) No single strategy showed any clear advantage compared with another 5) Comprehensive interventions were more effective than single interventions	1) Even small effect sizes can be clinically impressive 2) Chronic disease patients, including those with diabetes, hypertension, cancer and mental health problems especially benefited from interventions	1) Compliance interventions have been much too narrow and limited 2) Compliance interventions should be designed to address the broader spectrum of patient outcomes (including satisfaction, quality of life, empowerment e.g.)	1) Two health education axioms, that people learn in different ways and that a variety of teaching approaches increases learner interest, have been validated 2) The effects are of similar magnitude to those generally considered to be successful in medicine
Schedlbauer A et al., 2004 Hyperlipidaemia Search 1972-20003 8 studies 5943 patients	8 RCT	Review	Simplification drugs patient education/ information intensified care complex behavioral approach	1) Improved adherence: 3/8 studies 2) Improved adherence & outcome: 1/8 studies	1) The majority of studies did not increase adherence significantly by informing, reminding and motivating patients 2) Particular types of interventions did not seem to be more effective than others	At this stage, no adherence-enhancing intervention can be recommended in clinical practice	1) Measure adherence more detailed and reliable 2) RCT's with long-term follow up, combinations of adherence and outcome, rigorous methodology, sufficient power (and economic analyses) 3) New interventions with a more patient centered approach	Adherence rates were very variable, adherence rates in the control groups ranged from 23% to 94%

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Schroeder K et al., 2004 Hypertension Search 1975-2000 38 studies 1.5.519 patients	38 RCT	Review	Dosing simplification Patient education Patient motivation Complex interventions	1) Dosing simplification: effects 7/9 studies 2) Patient education: mostly unsuccessful 3) Patient motivation: effects 10/24 4) Complex interventions: effects 8/18 studies	1) Reducing the number of doses appears to be effective, although there is less evidence of an effect on blood pressure reduction 2) Some motivational strategies and complex interventions appear promising but we need more evidence on their effect through carefully designed RCT's	Reducing the number of daily doses should be tried as a first line strategy (although there is less evidence of an effect on blood pressure)	1) Larger trials of higher quality are needed that use reliable methods of measuring adherence and investigate the relationship between adherence and blood pressure reduction 2) Economic evaluations of interventions are needed	1) For complex interventions it is often difficult to estimate the independent effect of individual interventions 2) It remains difficult to disentangle specific adherence effects as opposed to non-specific effects of increased attention
Sharp J et al., 2005 Hemodialysis Search 1970-2003 16 studies 647 patients	1 RCT	Review	Psychological interventions	Psychological interventions appear to indicate some success	1) Psychological interventions to improve adherence to fluid intake restrictions appear to indicate some success in decreasing IWG = Interdialytic weight gain 2) The validity of these findings is circumscribed because of the study designs	If we wish to be more confident that psychological interventions are effective in improving adherence to fluid restrictions in hemodialysis patients, larger well-designed trials are required	1) Larger, well designed, controlled, multicenter trials 2) Research should consider applying cognitive behavioral techniques to renal population 3) Clearer description of intervention protocols	Combined interventions can enhance treatment effect, however, it is difficult to ascertain which technique is responsible for any detected change



First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Takiya LN et al., 2004 Hypertension Search 1970-2000 16 studies 2446 patients	16 RCT	Meta	Behavioral Educational Combination	1) Behavioral interventions: effect ES = 0.04 2) Educational interventions: heterogeneity 3) Combined interventions: heterogeneity	1) The ES (0.04) indicates a small non-significant improvement of adherence 2) Education and combined: no conclusions due to heterogeneity 3) Of behavioral interventions package change was most successful (ES 0.12) 4) No single intervention improved adherence over others	1) At this time there is no one particular intervention that provides a significant improvement in adherence rates to antihypertensives 2) A patient-specific approach should be modeled	More comparative RCT's are needed to determine the value of a given intervention. 2) Investigate the impact of various patient factors to fully understand the reasons for non-adherence	If patients do not believe in modern medications, do not view hypertension as a significant medical condition and hence do not value the medication their adherence may be affected
Van Dam HA et al., 2003 Diabetes Search 1980-2001 8 studies 1940 patients	8 RCT	Review	Patient directed interventions Provider directed interventions	Tentative conclusion is that patient directed interventions are more effective than provider directed interventions	The most effective interventions are those with a direct approach to support patients participation in diabetes care and self-care behaviour	Diabetes teams could consider to focus on programmes for directly enhancing patient participation in diabetes care	Well-designed intervention studies are needed on the effects of enhancing patient participation	Changing providers' consulting style into a more patient-centered one proves hard to sustain
Van der Wal MHL et al., 2005 Cardiovascular Search 1988-2003 48 studies	8 RCT	Review	Various interventions	Significant improvements of adherence in 12/12 studies	1) The outcomes of the review should be interpreted with caution 2) Evidence based interventions to improve compliance in patients with heart failure are scarce and need to be developed and tested	1) Targeting patients at risk 2) Recommended are patient related, regimen related and health care provider/ organisation related strategies	1) Interventions that can increase compliance need to be tested in RCT's 2) Research is needed to establish the optimal dose of the interventions required	1) From this review it is not clear which part of the interventions was most successful 2) Moreover, we do not know what the optimal dose or intensity of the intervention should be

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Van Eijken M et al., 2003 Various diseases (elderly) Search 1975-2001 14 studies 4196 patients	14 RCT	Review	Generalised single intervention Generalised combined intervention Tailored combined intervention	1) Generalised single: effects 3/13 interventions 2) Generalised combined: effects 1/3 interventions 3) Tailored combined: effects 3/7 interventions	1) More than half of the interventions had no effect 2) Telephone linked reminder systems achieved the most striking effect 3) Tailored combined interventions seemed to have more effects than single and generalised interventions	It might be worthwhile to aim at improving compliance to drug regimens in which non-compliance has the largest clinical consequences	1) Future research should include patient perspectives and shared decision making (concordance) 2) Methodological quality of RCT's needs improvement	We were not able to unequivocally define the contents of the interventions, because they were not described in sufficient detail
Vergouwen ACM et al., 2003 Depression Search 1966-2002 19 studies 5232 patients	19 RCT	Review	Patient education Collaborative care	1) Patient education: effects 2/5 studies 2) Collaborative care: effects: 9/11 studies	1) Educational interventions failed to demonstrate a clear benefit 2) Collaborative care interventions demonstrated significant improvements in adherence and were associated with clinical benefit	1) We found evidence to support the introduction of interventions to enhance adherence 2) Targeting only those patients with persistent symptoms (within 2 months) may be a viable option	Research should attempt to elicit the effects of individual components of collaborative interventions (to reduce avoidable costs)	Probably the improvements (in outcome) resulted from improved quality of care (prescribing) and improved adherence
Vermeire E et al., 2005 Diabetes Search 1966-2002 21 studies 4135 patients	14 RCT	Meta	Various interventions	1) Nurse led interventions: small effects 2) Home aids: small effects 3) Diabetes education: small effects 4) Pharmacist interventions: small effects 5) Change dosing/frequency: small effects	Current effort to improve adherence do not show significant effects nor harm	1) Whether any intervention enhances adherence effectively still remains unanswered 2) The majority of authors drew positive conclusions, but it is crucial to notice that significant differences were probably not very clinically relevant	1) The generally accepted methodological rules should be applied 2) Adherence should be defined explicitly and measured accordingly 3) Compliance research lacks economical evaluations	1) Educational interventions were so poorly described that it was impassible to discern differences or similarities between programmes 2) Many interventions were mistakenly called adherence interventions (instead of diabetes care)

First author	Number of RCT's	Review / Meta	Adherence Interventions	Results / Improvement	Authors' conclusions	Authors' recommendations for practice	Authors' recommendations for research	Authors' other remarks
Yildiz A et al., 2004 Depression Search 1976-2000 22 studies 1710 patients		Meta	Reduced daily dosing	No significant differences in drop outs were found between 1 or more daily doses	The results suggest that adverse events which are significant enough to result in drop-outs, are not more frequent with 1 daily dosing than multiple daily dosing	A simplified treatment regimen may be practical to increase treatment success rates in depression	Future trials will clarify if there is a particular group of patients for whom once or multiple dosing more beneficial, and if adverse events gives different results than the present report	The rates of drop-outs has limited utility when compared to the rates of adverse events, but numerical data on adverse events were not available
Zygmunt A et al., 2002 Schizophrenia Search 1980-2000 39 studies 3972 patients	33 RCT	Review	Individual treatment Family therapy Group therapy Community interventions Mixed interventions	1) Individual treatment: effects 2/4 studies 2) Family therapy: effects 3/12 studies 3) Group therapy: effects 0/2 studies 4) Community interventions: effects 3/6 studies 5) Mixed interventions: effects 3/9 studies	1) Overall, 13/39 studies (=33%) were effective 2) Psychoeducational interventions (only knowledge) were ineffective 3) Concrete instructions and problem-solving strategies are useful (behavioral) 4) Models of community care are promising 5) There was little relation between the duration/intensity and effectiveness. 6) No one specific intervention showed overwhelming success over others	1) Interventions should be adapted to the changing realities outside the hospital setting (after discharge) 2) Booster sessions are needed because adherence problems are recurring 3) We recommend that interventions continue for at least 18 months with quarterly assessment	1) Further theoretical development is needed 2) Subtypes of non-adherence (intentional versus unintentional etc.) should be assessed to assign patients to appropriate interventions	1) Multifaceted interventions makes it difficult to identify elements that contributed to success or failure of interventions 2) Adherence is typically seen as an individual treatment challenge, rather than one that is amenable to contextual influences and various service strategies. The complexity of these influences also complicates theory development



**Literature list included reviews**



## Literature list included reviews [1-38]

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37. Yildiz A, Pauler DK, Sachs GS: **Rates of study completion with single versus split daily dosing of antidepressants: a meta-analysis.** *J Affect Disord* 2004, **78**: 157-162.
38. Zygmunt A, Olfson M, Boyer CA, Mechanic D: **Interventions to improve medication adherence in schizophrenia.** *Am J Psychiatry* 2002, **159**: 1653-1664.



**Excluded reviews and reason for exclusion**



## Excluded reviews and reason for exclusion

<b>AUTHOR</b>	<b>REASON FOR EXCLUSION</b>
Allen J.P. et.al., 1992[1]	Descriptive review.
Ammassari A. et.al., 2002[2]	Factors related to adherence.
Anderson I.M. et.al., 1995[3]	Factors related to adherence.
Awad A.G. et.al., 2004[4]	Descriptive review.
Awad A.G., 2004[5]	Descriptive review.
Bacaltchuk J. et.al., 1999[6]	(New) medication/treatment effects.
Baldessarini R., 1994[7]	Descriptive review.
Barnes T. et.al., 2000[8]	Factors related to adherence.
Bartels D., 2004[9]	Factors related to adherence.
Berk M. et.al., 2003[10]	Factors related to adherence.
Bernard R.S. et.al., 2004[11]	Descriptive review.
Bernard-Bonnin A. et.al., 1995[12]	Outcome (without adherence).
Bhanji N.H. et.al., 2004[13]	(New) medication/treatment effects.
Bourbeau J. et.al., 2004[14]	(New) medication/treatment effects.
Brewer D.D. et.al., 1998[15]	Other: continued drug use.
Brown S.A. et.al., 1994[16]	Other: compliance is independent variable.
Brown S.A., 1999[17]	Other: development of diabetes education.
Brownell K.D. et.al., 1995[18]	Other: components of interventions.
Brownell K.D. et.al., 1995[19]	Descriptive review.
Brubacher D., 1994[20]	Descriptive review.
Brus H. et.al., 1997[21]	Factors related to adherence.
Bunzel B. et.al., 2000[22]	Factors related to adherence.
Burroughs T.E. et.al., 1997[23]	Factors related to adherence.
Caro J.J. et.al., 1999[24]	Other: geen review; een studie.
Cochrane M.G. et.al., 2000[25]	Magnitude of adherence.
Collingsworth S. et.al., 1997[26]	(New) medication/treatment effects.
Cooper A.F. et.al., 2002[27]	Factors related to adherence.
Coster S. et.al., 2000[28]	Outcome (in relation to adherence).
Cramer J.A., 2004[29]	Factors related to adherence.
Cramer M.P. et.al., 1994[30]	Other: compliance is independent variable.
Cuijpers P., 1998[31]	(New) medication/treatment effects.
De Young M., 1996[32]	Literature search/inclusion unclear.
Demyttenaere K., 1997[33]	Descriptive review.
Di Fabio R.P., 1995[34]	(New) medication/treatment effects.
DiMatteo M.R. et.al., 2000[35]	Factors related to adherence.
DiMatteo M.R. et.al., 2002[36]	Outcome (without adherence).
DiMatteo M.R., 2004[37]	Descriptive review.
DiMatteo M.R., 2004[38]	Magnitude & factors related to adherence.
DiMatteo M.R., 2004[39]	Descriptive review.
Dornan M. et.al., 1998[40]	Literature searches & inclusion unclear.
Dunbar J.J. et.al., 1991[41]	Inclusion criteria primary studies?
Dunbar-Jacob J. et.al., 2001[42]	Descriptive review.

Elasy T.A. et al., 2001[43]	Other: Taxonomy of interventions.
Epstein L.H. et.al., 1996[44]	Other: (New) medication/treatment effects.
Fain J.A. et.al., 1999[45]	Gaps in patient education research.
Fenton W.S. et.al., 1997[46]	Inclusion criteria unclear.
Fish L. et.al., 2001[47]	Descriptive review.
Fogarty L. et.al., 2002[48]	Descriptive review.
Fotheringham M.J. et.al., 1995[49]	Factors related to adherence.
Frank E., 1997[50]	Descriptive review (opinion).
Furukawa T.A. et.al., 2001[51]	(New) medication/treatment effects.
Gallant M.P., 2003[52]	Factors related to adherence.
Gibson P.G. et.al., 2002[53]	Outcome (without adherence).
Gibson P.G., 2001[54]	Outcome related to self-management.
Gray R. et.al., 2002[55]	Descriptive review.
Griffin K.J. et.al., 2001[56]	Factors related to adherence.
Griffith S., 1990[57]	Factors related to adherence.
Hack S. et.al., 2001[58]	Magnitude of adherence.
Haddad M. et.al., 2000[59]	Other: one study.
Hailey B.L. et.al., 2000[60]	Factors related to adherence.
Hampson S. et.al., 2001[61]	Outcome (without adherence).
Haynes R.B. et.al., 1996[62]	Updated in 2005
Haynes R.B. et.al., 2002[63]	Updated in 2005.
Hellewell J.S., 2002[64]	Patients' satisfaction with drug treatment.
Hotopf M. et.al., 1997[65]	(New) medication/treatment effects.
Houlihan D.D. et.al., 1992[66]	Literature searches & inclusion unclear.
Hughes C.M., 2004[67]	In/exclusion primary studies unclear.
Hummer M. et.al., 1996[68]	Factors related to adherence.
Hussar D.A., 1994[69]	Literature search & inclusion unclear.
Inzucchi S.E., 2002[70]	(New) medication/treatment effects.
Ismail K. et.al., 2004[71]	Outcome (without adherence).
Jackson L. et.al., 2005[72]	Factors related to adherence.
Jelalian E. et.al., 1998[73]	(New) medication/treatment effects.
Kampman O. et.al., 1999[74]	Factors related to adherence.
Kaul V. et.al., 2000[75]	Factors related to adherence.
Keith S.J. et.al., 2003[76]	Factors related to adherence.
Kerse N. et.al., 2004[77]	One study.
Kjellgren K.I. et.al., 1995[78]	Descriptive review of interventions.
Kyngas H.A. et.al., 2000[79]	Factors related to adherence.
Lacro J.P. et.al., 2002[80]	Factors related to adherence.
Laederach H.K. et.al., 2000[81]	Factors related to adherence & outcome.
Lafeuillade A., 2001[82]	(New) medication/treatment effects.
LaRosa J.H. et.al., 2000[83]	Factors related to adherence.
Lemanek K.Ll et.al., 2001[84]	Descriptive review.
Loghman-Adham M., 2003[85]	Factors related to compliance.
Lorig K. et.al., 1993[86]	Series of studies.
Maramba G.G. et.al., 2002[87]	Factors related to adherence.

Marks R. et.al., 2005[88]	Factors related to adherence.
Marland G.R., 1999[89]	Descriptive review.
Masand P.S., 2003[90]	Adverse events.
McDonald H.P. et.al., 2002[91]	Updated version 2005 included.
Mekechuk J., 2004[92]	Factors related to adherence.
Meyerowitz B.E. et.al., 1998[93]	Factors related to adherence & outcome.
Milgrom H. et.al., 1997[94]	Descriptive review.
Miller N.H., 1997[95]	Descriptive review.
Montgomery S.A. et.al., 1995[96]	(New) medication/treatment effects.
Moore H. et.al., 2004[97]	Outcome (without adherence).
Morris L.S. et.al., 1992[98]	Literature search & inclusion unclear.
Morris L.S. et.al., 1993[99]	Factors related to adherence.
Mullen P.D. et.al., 1997[100]	Prevention.
Murray M.D. et.al., 2004[101]	Descriptive review.
Nagasawa M. et.al., 1990[102]	Factors related to adherence.
Nichol M.B. et.al., 1999[103]	Other: methodology of compliance research.
Nicholas M.K., 1995[104]	Factors related to adherence.
Norris S.L.L. et.al., 2002[105]	Outcome (without adherence).
Oehl M. et.al., 2000[106]	Descriptive review.
Oldridge N.B., 1991[107]	Magnitude of adherence.
Oomen J.S. et.al., 1999[108]	Factors related to adherence.
O'Shea B., 1995[109]	Descriptive review.
Osterberg L. et.al., 2005[110]	Descriptive review.
Park-Wyllie L.Y. et.al., 2003[111]	Descriptive review.
Partridge A.H. et.al., 2002[112]	Factors related to adherence.
Passalacqua G. et.al., 2004[113]	Outcome (without adherence).
Pastors J.G. et.al., 2003[114]	Outcome (without adherence).
Perkins D., 2002[115]	Factors related to adherence.
Rand C.S. et.al., 1994[116]	Other: measure adherence.
Rand C.S., 1993[117]	Other: measure adherence.
Read T. et.al., 2003[118]	Other; measure adherence.
Reis B.F. et.al., 1999[119]	Factors related to adherence.
Renders C. et.al., 2001[120]	Outcome (without adherence).
Rich M.W., 1999[121]	Prevention.
Riesen W.F. et.al., 2004[122]	Magnitude of adherence.
Rietveld S. et.al., 2002[123]	Factors related to adherence.
Rudd P., 1995[124]	Factors related to adherence.
Rusch N. et.al., 2002[125]	Factors related to adherence.
Ryan A.A., 1999[126]	Factors related to adherence.
Santarasci B. et.al., 2003[127]	(New) medication/treatment effects.
Schmier J.K. et.al., 1998[128]	Literature search/inclusion unclear.
Schroeder K. et.al., 2004[129]	Cochran version included.
Sclar D.A. et.al., 1994[130]	Factors related to adherence.
Shikiar R. et.al., 2004[131]	Other: satisfaction with medication.
Short S.D. et.al., 1996[132]	Other: theories on adherence.

Siafakas N.M., et.al., 1992[133]	Outcome (without adherence).
Sockrider M.M. et.al., 1996[134]	Factors related to adherence.
Spector S., 2000[135]	Factors related to adherence.
Squier R., 1990[136]	Factors related to adherence.
Stark M.J., 1992[137]	Factors related to adherence.
Steed L. et.al., 2003[138]	(New) medication/treatment effects.
Steele R.G. et.al., 2003[139]	Factors related to adherence.
Steiner J.F. et.al., 1997[140]	Other: measure adherence.
Stockwell Morris L. et.al., 1992[141]	See Morris & Schultz, 1992
Stuart B. et.al., 2002[142]	Other: inappropriate prescriptions.
Szeto A.Y.J. et.al., 1997[143]	Literature search/inclusion unclear.
Tang J.L. et.al., 1998[144]	(New) medication/treatment effects.
Tang J.W. et.al., 2004[145]	Outcome & transmission of drug-resistance.
Tashkin D.P., 1995[146]	(Regime) Factors related to compliance.
Thurston M. et.al., 2004[147]	Descriptive review.
Tollefson G.D., 1993[148]	(New) medication/treatment effects.
Tracqui A. et.al., 1995[149]	Other: measure adherence.
Trotta M.P. et.al., 2002[150]	Descriptive review.
Tsuyuki R.T. et.al., 2001[151]	(Medication) factors related to adherence.
Tuldra A. et.al., 2002[152]	Literature search/inclusion unclear.
Turk D.C. et.al., 1991[153]	Descriptive review.
Turpin R.S. et.al., 2004[154]	Literature search/inclusion unclear.
Uldry C. et.al., 2000[155]	Descriptive review.
Urquhart J., 1994[156]	Other: measure compliance.
Urquhart J., 1998[157]	Descriptive review.
Urquhart J., 2000[158]	Other: delivery systems.
Van Schaik D.J. et.al., 2004[159]	Factors related to adherence.
Van Tulder M. et.al., 2000[160]	Outcome (without adherence).
Vermeire E. et.al., 2001[161]	Factors related to adherence.
Vik S.A. et.al., 2004[162]	Factors related to adherence.
Volmink J. et.al., 1997[163]	Other: Africa / tuberculosis.
Waeber B. et.al., 1997[164]	Factors related to adherence.
Walker G.R., 1993[165]	Factors related to adherence.
Webber G., 1990[166]	Other: patient education.
Weingarten S. et.al., 2002[167]	Guideline adherence.
Weiss R.D., 2004[168]	Descriptive review.
Wetzels G.E.C. et.al., 2004[169]	Other: relation adherence - outcome.
Wiebe J.S. et.al., 1996[170]	Factors related to adherence.
Wielandt T. et.al., 2000[171]	Factors related to adherence.
Wierzbicki M. et.al., 1993[172]	Factors related to drop-out.
Wing R.R. et.al., 2002[173]	Other: mediating role of adherence.
Woodard C.M. et.al., 2001[174]	Descriptive review.
Worth H. et.al., 2004[175]	Descriptive review.
Zeller A. et.al., 2002[176]	Factors related to adherence.



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2. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P *et al.*: **Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature.** *J Acquir Immune Defic Syndr* 2002, **31 Suppl 3**: S123-S127.
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10. Berk M, Berk L: **Mood stabilizers and treatment adherence in bipolar disorder: addressing adverse events.** *Ann Clin Psychiatry* 2003, **15**: 217-224.
11. Bernard RS, Cohen LL: **Increasing Adherence to Cystic Fibrosis Treatment: A Systematic Review of Behavioral Techniques.** *Pediatr Pulmonol* 2004, **37**: 8-16.
12. Bernard-Bonnin A, Stachenko S, Bonin D, Charette C, Rousseau E: **Self-management teaching programs and morbidity of pediatric asthma: a meta-analysis.** *J Allergy Clin Immunol* 1995, **95**: 23-41.
13. Bhanji NH, Chouinard G, Margolese HC: **A review of compliance, depot intramuscular antipsychotics and the new long-acting injectable atypical antipsychotic risperidone in schizophrenia.** *Eur Neuropsychopharmacol* 2004, **14**: 87-92.

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17. Brown SA: **Interventions to promote diabetes self-management: state of the science.** *Diabetes Educ* 1999, **25**: 52-61.
18. Brownell KD, Cohen LR: **Adherence to dietary regimens 1: An overview of research.** *Behav Med* 1995, **20**: 149-154.
19. Brownell KD, Cohen LR: **Adherence to dietary regimens 2: Components of effective interventions.** *Behav Med* 1995, **20**: 155-164.
20. Brubacher D: **Aspects of compliance: A review.** *Journal of Pharmaceutical Medicine* 1994, **4**: 31-39.
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43. Elasy TA, et al.: **A taxonomy for diabetes educational interventions.** *Pat Educ Couns* 2001, **43**: 121-127.
44. Epstein LH, Coleman KJ, Myers MD: **Exercise in treating obesity in children and adolescents.** *Med Sci Sports Exerc* 1996, **28**: 428-435.
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**SPECIAL SUPPLEMENT: Measurement of adherence**



## **SPECIAL SUPPLEMENT**

### **Measurement of adherence**

#### **Introduction**

- 1. Are different adherence measures used in the two review-sets?**
- 2. Pros and cons of adherence measurement tools**
  - direct observable behavior
  - subjective self-reports
  - objective monitoring of medication usage
  - objective physiological/biomedical measures
  - health outcomes
  - combined adherence measurements
- 3. Conclusions and final remarks**
- 4. Overview of adherence measurement per review**

#### **Reference List**

## Introduction

In this report, two sets of reviews were distinguished: 23 reviews with significant differences in effectiveness between adherence interventions, and 15 reviews without significant differences in effectiveness between adherence interventions. Many review authors complain about the quality of the primary studies and about the poor measurements of adherence in the primary studies [1,2] or the frequent use of subjective measures of adherence [3]. Thus, the question is, are different adherence measures used in the two sets of reviews? If so, it could be an explanation for the differences between the two sets of reviews, because it is well known that many adherence measures are not accurate or even unreliable. Therefore, the aim of this special supplement is:

- 1) *To analyze whether or not the two sets of reviews (23 and 15) differ in respect with adherence measurements.*
- 2) *To give an overview of the pros and cons of the adherence measurement tools which were used in the reviews.*

This supplement is based on the 38 included reviews and on a selection of special reviews on measurement tools or measurement methods to assess adherence [4-20] (n.b. see Rand and Whise for a tabulated overview of the pros and cons of the various methods to assess adherence to Asthma Medication Regimens ) [12].

### 1. Are different adherence measures used in the two review-sets (23 and 15)?

To detect possible differences between the two sets of reviews, we have made a tabulated overview of the adherence measurements which were used in each of the 23 respectively 15 reviews. The last six pages of this supplement show the tabulated overview. We have counted the number of reviews with a variety of adherence measures and the number of reviews with one particular kind of adherence measure. Table 1.1 gives the results.

Table 1.1 The adherence measurements in the two sets of reviews (23 and 15)

<i>adherence measures</i>	<b>23 reviews with significant differences <i>number</i></b>	<b>15 reviews without significant difference <i>number</i></b>
- Various adherence measures	18	12
- Attendance/drop-outs	3	1
- Electronic Monitoring devices (EM)	1	0
- Refill/pill count	0	1
- Weight gain	0	1
- Not reported	1	0
Total	23	15

Most frequently, a variety of adherence measures was used in both sets of reviews. In the first set 78% of the reviewers (18/23) included various adherence measures and in the second set 80% of the reviewers (12/15) included various adherence measures (see the details in the tabulated overview). A minority of the reviews was restricted to one particular kind of adherence measure, for example attendance/drop-outs (3/23 and 1/15), EM-devices (1/23 and 0/15) or other measures (1/23 and 2/15).

We must conclude that there are no indications that the differences between the two sets of reviews can be explained by the adherence measures used in the two sets of reviews.



## 2. Pros and cons of adherence measurement tools

Table 2.1 gives an overview of all the adherence measures and measurement tools used in the primary studies of the 38 included reviews. We have categorized the measures in five clusters, derived from Roter's classification [21]: direct observable behavior, subjective self-reports, objective monitoring medication usage, objective physiological or biomedical measures, and, finally, health outcomes.

Table 2.1 Overview of adherence measures in the 38 included reviews

<i>Direct observable behavior</i>	<i>Subjective (self-) reports</i>	<i>Objective monitoring medication usage</i>	<i>Objective Physiological/Bio-medical measures</i>	<i>Health outcome</i>
Attendance Appointments Drop out e.g.	Questionnaire Self-monitoring - diaries - checklists - (food) records, - (hand)computers Interview Physician reports	Refill (records) Pill counts Bar-code scanner* Electronic monitoring devices (EM)	Tracer substances Blood sugar Hemoglobin Weight Blood pressure Cholesterol e.g. Vitalog** Accelerometers***	Functional status Well being Quality of life Hospitalization Morbidity Mortality

\*) Bar-code scanners: patients are instructed to scan the bar-code of the medicine bottle every time the medicine is taken.

\*\*) Vitalog is a microprocessor that measures heart rates (to measure exercise compliance).

\*\*\*) Accelerometers measure movement produced by skeletal muscles.

Before turning to the pros and cons of the various adherence measures, it should be said that - according to nearly all adherence experts - an agreement on the golden standard in measuring adherence does not exist and all measurements have their limitations [1,4,10,13,18,19,22-24]

### Direct observable behavior

Directly observable behavior or therapy do not cause any problems in the assessment of adherence.

Attendance for example, or keeping appointments are a highly visible kind of adherence behavior [25]. Monitoring attendance is clearly an adequate way of measuring compliance to supervised administration of care or the use of (preventive) tests or services [26].

There is a difference between appointment making and appointment keeping. Intervention studies using appointment making as outcome measure showed substantially larger effects than those using appointment keeping. Encouraging appointment making appears easier than achieving appointment keeping. There is a variety of external issues affecting utilization, including barriers such as transportation, costs and competing time demands. Appointment making may reflect patients' desire to cooperate with the recommendations to seek care, but their inability to follow through when faced with practical barriers [21].

Direct Observable Therapy (DOT) means that the therapy is delivered directly by a health care professional, for example injection or intravenous infusion. In asthma therapy, observing and assessing patient's skill in the use of a metered-dose inhaler has been used as a measure of adherence to proper technique [15]. Sometimes Direct Observable

Therapy might be the only solution when poor compliance creates major medical and social concerns, for example the emergence of drug-resistant bacterial strains [4].

Perhaps the closest to a golden standard measure of compliance was the use of direct observation via closed-circuit television to validate electronic monitoring methods. However, this method is not representative and could also impossibly be implemented in routine use [18].

Direct observable assessments of adherence - such as attendance or appointment keeping - are accurate measures of adherence, but limited in applicability. They are not accurate methods for measuring adherence to self-administered (non-supervised) medications or tests [26].

### **Subjective self-reports**

Subjective measures of adherence are widely used. Self-reports are the simplest and least equipment-intensive methods to assess compliance and they can be useful in clinic interviews and large-scale studies [15]. Patients' self-reports are fast, simple and inexpensive, but of variable validity, based on demand characteristics of the environment and limited by patients' memory [12].

Self-reports in intervention studies may contribute to confusing results. They are known to overestimate adherence. In the case of intervention studies, self reports may have contributed to overestimation of the success of the interventions [27] but also to underestimation of the effect of interventions [28]. Such subjective measures of adherence could easily blur any differences between groups [29]. According to Urquhart, self-reporting is so affected by favorable bias and confounded by forgetfulness on the part of the patient that it is surprising that investigators continue to rely upon it [18]. In self-reports, a distinction can be made between a) questionnaires, b) self-monitoring c) interviewing.

#### *a) Questionnaires*

Many intervention-studies make use of questionnaires to assess patients' adherence, but structured questionnaires (on food intake) for example, are susceptible to biases [7]. Patient self reports may be erroneous because patients may forget about doses taken or missed [13,30]. The biasers that appear most prominent in distorting estimates of dietary intake from structured questionnaires are social desirability and social approval, both of which however, can be measured (and controlled for) [7].

When we measure adherence in intervention studies, the potential effect of the measurement itself, termed the 'Hawthorne effect' must be considered. This is the effect (often beneficial or positive) of the observation itself on the outcome [10].

According to Burke [31], progress has occurred in the development of psychometrically sound instruments to measure adherence or factors related to it. Some examples are [31]:

- a four item questionnaire to address barriers to medication taking<sup>1</sup>,
- scales to assess psychological barriers to regimen compliance (hypertension)<sup>2</sup>,
- self-efficacy scales in respect with adherence to a cholesterol lowering diet<sup>3</sup>,

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<sup>1</sup> Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care* 1986; 24:67-74.

<sup>2</sup> Hill MN, Berk RA. Psychological barriers to hypertensive therapy adherence: Instrument development and preliminary psychometric evidence. *Cardiovascular nursing* 1995; 31: 37-43.

<sup>3</sup> Burke LE, Ewart CK, Thompson PD et.al. Psychometric evaluation of the cholesterol-lowering diet self-efficacy scale. *Circulation* 1995; 92 (Suppl. 8): 66.

- reducing weight<sup>4</sup>,
- taking medication<sup>5</sup>.

Two questionnaires are recommended for asthma medication [12]:

- the Medication Adherence Scale
- the Inhaler Adherence Scale<sup>6, 7, 8</sup>

Some scales have established content validity [23] for example:

- the two four-item self-report scales from Brooks et al<sup>9</sup> [15].
- the Heart Failure Self Care Behaviour Scale<sup>10</sup>
- the Compliance Questionnaire<sup>11</sup>

#### *b) Self-monitoring*

Self-monitoring is very common in self-management of chronic diseases and widely used. Increasingly, patients are taught self-care and self-management skills to cope with their disease. Patients' self-management, however, must be distinguished from self-monitoring as a measurement tool to assess patients' adherence. Measurement tools to assess adherence usually are diaries or (computerized) daily checklists and, increasingly, hand-held computers.

Diaries can provide a detailed account of patient adherence [12]. An advantage of diaries or written logs is that they circumvents the bias of recall, but keeping a diary requires training and cooperation of the participant [31]. Patient adherence to diaries over time, is frequently poor (many patients stop or refuse). Patient diaries have also been shown to be inaccurate [13] and the data are vulnerable to patient deceit [12]. Diary cards give only an illusion of objectivity, for it is impossible to know when the cards were filled out or how truthful a representation of reality they are [18]. According to Schmier, 'phantom readings' were found in self reported diary flow rates (in asthma) that were not detected by the peak flow monitor [15].

Besides diaries, four self-report methods for assessing adherence to dietary regimens or food intake exist: 24-hour recall, food records, food frequency questionnaires and the diet history [31]. Issues of concern common to all self-report measures include validity and sources of respondent error, either non-deliberate errors in recall or deliberate errors of misreporting [31].

The use of hand-held computers for self-monitoring is promising, particularly when an accurate assessment of compliance to the recording process is required or when accuracy of the recording schedule is important. Moreover, the hand-held computer offers an attractive alternative to paper and pencil diaries [31].

<sup>4</sup> Glynn SM, Ruderman AJ. The development and validation of an eating self-efficacy scale. *Cognitive Therapy and Research* 1986; 10: 403.

<sup>5</sup> De Geest S, Abraham I, Gemoets H, Evers G. Development of the long-term medication behaviour self-efficacy scale: Qualitative study for item development. *Journal of Advanced Nursing* 1994; 19: 233-238.

<sup>6</sup> Kinsman RA, Dirks JF, Dahlem NW. Noncompliance to prescribed-as-needed (PRN) medication use in asthma: usage patterns and patient characteristics. *J Psychosom Res* 1980; 24: 97-107.

<sup>7</sup> Dolce J, Crisp C, Manzella B, Richards JM, Hardin M, Bailey WC. Medication adherence patterns in chronic obstructive pulmonary disease. *Chest* 1991; 99: 837-41.

<sup>8</sup> Bailey WC, Richards JM, Brooks CM, Soong S, Windsor RA, Manzella BA. A randomized trial to improve self-management practices of adults with asthma. *Arch Intern Med* 1990; 150:1664-8.

<sup>9</sup> Brooks CM, Richards JM, Kohler CL et.al. Assessing adherence to asthma medication and inhaler regimens: a psychometric analysis of adult self-report scales. *Med Care* 1994; 32: 298-307.

<sup>10</sup> Jaarsma T, Abu-Saad HH, Dracup K, Halfens R. Self-care behaviour of patients with heart failure. *Scand J Caring Sci* 2000; 14: 112-9.

<sup>11</sup> Evangelista LS, Berg J, Dracup K. Relationship between psychosocial variables and compliance in patients with heart failure. *Heart Lung* 2001; 30: 294-301.

### c) Interviewing

Much has been remarked on interview-methods to assess adherence, because interviewing is of particular relevance in daily clinical practice.

Questioning patients is the most widely applicable method for evaluating compliance. Because it is simple and cheap, it should be routine [4,14]. Direct questioning of patients can be used to elicit honest responses and it can be highly beneficial [13]. According to Myers, patients can be very accurate in reporting the likelihood that they will adhere to treatment if they are asked simply and directly [9]. Careful questioning might identify over half of the non-compliers. Interview alone sometimes produces better results than the combination of self-report, biochemical test, and urinary drug-level measurement [4]. Patients are accurate when they say that they have not taken their medication. However, objective records do not often confirm the verbal records of people who state that they have taken their medication as prescribed [9,14].

One of the problems is that doctors do not often explicitly ask if patients have taken their drugs and patients rarely *volunteer* admitting to their doctor not having taken their drugs [21]. And when asked, patients may give socially desirable answers [19,23] or they want to please their physician or to earn their approval [11,32]. An alternative is to ask patients to estimate the percentage/number of tablets they have missed during a defined time interval or the frequency of deviation from their prescribed regimen (eg. rarely, occasionally, often) [19].

According to Haynes, most adherence problems can be detected by three simple maneuvers, used in sequence [6]:

- 1) watch for patients who fail to (or irregular) attend appointments;
- 2) watch failure to respond to treatment;
- 3) ask these patients about their adherence. About half of the non-adherers will admit on direct questioning. This simple clinical measure appears to have a sensitivity of 55% and a specificity of 87% ("during the last week, have you missed any tablets?") [6]. Other ways of assessing adherence are not practical in most clinical settings but are possible - and often necessary - in research settings [6].

Doctors tend to substantially overestimate adherence [8,9,11,14]. They are poor in judging patient adherence, because they often fail to discuss with patients their patterns of medication use adequately. Physicians are more successful in identifying adherence problems when they use an information-intensive approach (e.g. "What medications are you taking now? And are you taking them now? How often do you take them? Have you noticed any side effects? Have you noticed anything unusual caused by them?"). Rand recommends the physician to openly discuss the potential problems in maintaining good adherence over long periods of time, encouraging a clinical relationship that allows patients to feel comfortable in acknowledging their own difficulties with the prescribed regimen [11].

The quality of the relationship between patients and the clinical staff influences the reliability of data from interviews [4]. One way of increasing the accuracy of responses to direct questioning is to establish trust between the surveyor and the respondent. However, trust is certainly not a sole determinant of telling about non-compliance. Trust will not necessarily imply that patients will give honest responses to potentially embarrassing questions. Patients may be reluctant to admit 'bad' behavior [10]. In fact, the lack of willingness to admit 'incorrect' behavior may be present even more in cases where trust does exist than where there is no relationship et al [13].

Not only in clinical practice, but also in intervention studies, a social desirability effect may occur. The higher regard the respondent has for the authority, the stronger this social desirability effect could be. "Patients who participate in educational interventions might wish to please study staff by reporting the behavior changes that the staff are clearly looking for" [32].

Rittenhouse describes an interview technique that estimates compliance levels in populations rather than in individual patients [13]. The Randomized Response Interview (RRI) is a new method to estimate compliance. The RRI approach allows people to admit non-compliance in a non-embarrassing way. This technique has been used in surveys of deviant or criminal behavior [13].

### **Objective monitoring medication usage**

There are three methods to assess adherence to medication taking behavior: a) Electronic Monitoring (and bar-code technology), b) pill counts and c) prescription refill assessments.

#### *a) Electronic Monitoring (EM)-devices*

Several forms of EM-devices exist. The first device in this category was an eyedrop dispenser in which the time- and date-stamped event was coincident cap removal and bottle inversion. For oral dosage forms there are simple cup-type drug containers with a microswitch or blister package generating a signal when a blister is broken into. For inhalational drugs, microswitches are actuated by the drug dispensing mechanism [33]. There are also devices that remind patients (auditory and visually) when it is time to take their medication, the 'MedMinder' [17].

Bar-code technology means that the patient scans the bottle each time the medication is taken. This method requires the patient to remember to use the scanner. The particular value is that it allows for an indication of the number of pills taken [31].

Compliance measured by Electronic Monitoring (EM) devices is the most accurate compliance assessment method to date, because the time and date of actual dosing events is being recorded [9,16,30]. EM-devices are able to detect the 'toothbrush effect' or 'white-coat compliance' that is, increased compliance just before and just after appointments with the health care staff [4,13,18]. Similarly, drug 'holidays' and 'dumping medication' may be detected. Dumping is the phenomenon in which patients dispose large quantities of medication prior to an appointment to present the appearance of compliance [15].

However, even EM is not entirely accurate because opening the EM unit to remove a tablet or release a spray does not necessarily mean that the dose was taken [9,10,13,23,30]. Therefore, Morrison states that using an EM-device is an objective and reliable method of measuring vial opening, but it is an indirect measure of adherence [34]. However, patients generally do not create a false record of good compliance by means of regular bottle-opening [4].

A restriction of this method can be that patients who are very compliant or have a positive attitude toward medication taking are possibly more motivated to give consent to data-collection with MEMS than patients who are non-compliant [23]. Although electronic monitoring unbeknownst to the patient would provide a more accurate appraisal of compliance, this approach is ethically unsound [15].

Interestingly few patients object when compliance measurement is proposed and its rationale explained [18]. About 70% of patients acknowledged that they sometimes deviated from the doctor's instructions, but they rarely informed their doctor about these deviations. However, these patients agreed strongly that the doctor should know about these deviations, and they accepted the idea of a device to record and convey that information to the doctor [18].

Availability and the cost of these devices limit the feasibility of this approach in ambulatory settings [13,19] and the effort and time necessary to obtain measurements [16]. But, according to Urquhart, the cost of micro circuitry has fallen drastically and memory capacity of EM-devices has grown since 1987 [18].

#### *b) Pill counts*

Pill counts (or canister weights) are being used to estimate patient compliance. It means that the remaining pills in the bottle are being counted at the end of a designated time interval to calculate the degree of adherence. Canister weight also estimates compliance through the weight of medication remaining in the canister or bottle.

Manual pill-count, though simple and cheap, do not always accurately reflect patients' compliance [4,10,13,15,19]. Pill counts may result in an overestimation of adherence [9], because patients may choose to discard or hoard untaken doses [15,18] and medication which is not in the container was not necessarily taken appropriately and may not have been taken at all [15]. Because counting pills is vulnerable to patient manipulation, one author attempted to increase reliability of this method by performing unexpected visits to patients' homes for surprise pill counts [1].

Besides, this method is often erroneous because patients do not always return bottles that have pills remaining [30]. Also, Patients who fail to return their pill bottles cannot be evaluated at all, suggesting the possibility that this method may be skewed toward the more compliant [15]. Some patients however refuse to submit to pill counts [13].

Compared to newer methods, such as electronic monitoring of pill use or chemical markers, traditional methods as refill-records, patient self-report and pill count have been shown to overestimate adherence [1].

#### *c) Prescription refills*

Three parameters characterize prescription refill data: single versus multiple refill intervals, assessment of medication availability versus gaps in treatment and, continuous versus dichotomous distributions [16]. Prescription refill rates can be a relatively effective method for tracking compliance in situations involving a single or unified pharmacy system. The fact that compliance rates can be estimated without patients' awareness is an advantage of this approach, increasing the accuracy of the estimates by eliminating any Hawthorn effect [10,15]. Patterns of ongoing prescription filling probably provide the most accurate estimate of actual medication use in large populations [10] to assess drug exposure retrospectively or when direct measurement of medication consumption is not feasible [16].

The convergent validity of refill data has been assessed in a number of studies. Steiner found that refill compliance correlated significantly with other compliance behaviors (such as appointment keeping or medication consumption) in most studies. The correlations are of moderate strengths ( $r = 0.2 - 0.7$ ). Most studies also found moderate correlations between refill compliance and serum drug levels or drug effects such as blood pressure [16].

The limitation of prescription refill data to measure compliance is that refill data cannot

assess the timing of doses [16,19]. Prescription refills do not absolutely translate to a patient's consumption of the drug [10].

Intervention studies using refill records as the outcome measure showed substantially larger effects than pill count. Filling prescriptions demand only limited commitment and may more accurately reflect the intention to comply than actual compliance. This suggests that people fill their prescriptions more readily than that they consume their medicine [21]. Many patients request refills regularly when reminded, even if they have not run out of drug, whereas others stockpile medications or have quantities of medications in several areas for convenience [9,30].

Prescription refill data have been primarily used to estimate adherence concerning drugs taken for chronic illnesses such as hypertension. They are not useful for medication taken for short periods if subsequent refills are not required (e.g. antibiotics) [16,19].

### **Objective physiological/biomedical measures**

Biochemical analysis of blood, urine, or other bodily excretions to objectively measure medication is the only method of adherence measurement that confirms that medications have actually been taken by the patient, and for this reason, biochemical analysis is one of the most valuable techniques available for assessing adherence [12]. Blood or urine levels offer a perceived golden standard of compliance [13].

Clinical examination might indicate that the medication has been ingested. Serum cholesterol can be considered as an important marker of adherence to lipid lowering medication [1]. Other examples are: normalization of blood pressure in hypertension, disappearance of fever with antibiotics, decreased intraocular pressure in glaucoma, and so on. When clinical examination does not detect such expected improvements, poor compliance is a possible explanation [4]. According to Morrison, blood pressure or weight gain are considered to be objective and reliable endpoints although other factors than adherence may contribute to these effects [35]. Three biochemical measures can be used to assess adherence to smoking cessation. Serum or plasma cotinine levels have the highest sensitivity and specificity of the three measures. A disadvantage is the intrusiveness of the method and financial requirements [31,36].

Medication may also be coupled with a chemical marker to be detected in a biological material such as blood, urine, stools e.g. Compliance can be assessed by subsequent measurement of the marker in plasma [4,18]. Low dose marker methods unequivocally demonstrate drug ingestion. According to Urquhart, 'the marker methods' have been invaluable research tools [18].

For drugs with long elimination half-lives, measured concentrations of drug in plasma can be a useful marker of compliance [18]. However, the plasma half-life of most drugs is only a fraction of a day. Thus the plasma concentration reflects drug administration only during the previous day or so [15,18,27]. Thus even if numerous doses were omitted but a few doses were taken immediately before the blood test (white coat compliance), the result would show the presence of a moderate amount of drug [4,30]. The data provide no information about the overall rate and pattern of compliance over time [15].

Other disadvantages are connected with biochemical measurements. For example, the methods may be invasive/intrusive for patients, and costly and not always possible, feasible or appropriate [12,13,19,23]. There are genetic differences in how individuals absorb and metabolize drugs [9]. Drug or metabolite levels may vary widely because of individual pharmacokinetics (i.e. rates of absorption, distribution, metabolism, and excretion) [10,37]. Besides, the costs of such tests may be prohibitive for routine use

outside a research setting [10]. Their use in routine care would be limited to clinical settings where non-compliance, unchecked, is responsible for serious clinical problems [18].

Finally, adding chemical tracer substances to drugs causes ethical concerns [19]. Besides, "such techniques also implicitly reject patient self-report, taking a stance that now seems paternalistic and outdated" [37].

#### *Other objective measures*

Other objective measurement tools for (exercise) adherence measure bodily movements. There are types of accelerometers that measure movements produced by skeletal muscles and resulting in energy expenditure, which provides an objective and direct measure of frequency and intensity of physical activity [31]. The Vitalog is a microprocessor that measures and sequentially stores heart rates. Such electronic monitors, while expensive and thereby unavailable on a widespread basis, provide an assessment of the temporal patterns of adherence [31].

### **Health outcomes**

Health outcomes are not considered to be an accurate measure of adherence, according to nearly all the review authors. Some citations may illustrate their findings.

#### *A weak relation between adherence and outcome*

"Health outcome can be an indication of adherence, but the relation between adherence and health outcome is often a weak one and sometimes even absent"[38].

"Outcome measures can be useful in identifying patients who fail to reach treatment goals. A major difficulty however, is the unclear relationship between adherence and outcome. Changes in outcome might not be particularly responsive to changes in adherence" [9].

#### *Few research findings*

"Few studies of cancer patients have evaluated the relationship between adherence levels and achievement of the treatment goal" [10]. And, "surprisingly little is known about the relationship between adherence (to asthma therapy) and outcomes [15]. Also, little is known about the optimum level of adherence; what level of adherence is 'enough' and for whom?" [15].

#### *Other factors interfere*

"As many factors, other than adherence may influence clinical outcomes, it has been argued that the therapeutic response alone should not be used to conclude whether subjects are taking their medication as prescribed" [19].

#### *Inaccurate measurements of adherence*

"Inaccuracy of self-report also might explain the absence of improved outcomes in the face of apparent increased adherence" [32].

"Several factors make it difficult to demonstrate associations between non-adherence and selected health outcomes. Besides the inherent difficulties in accurately measuring drug adherence, many other factors, such as life style (eg. diet, alcohol use) and the appropriateness of the drug regimen may also affect therapeutic efficacy"[19].

#### *Over-adherence*

Finally, a frequently overlooked problem - and one that may be more of an issue in the care of oncology patients than of other patients - is over-adherence to self administered medication. A 'more is better' approach or confusion resulting in overuse of a drug has



been documented in studies of other diseases and may, in the case of oral chemotherapy, lead to substantially increased toxicity [10].

### **Combined adherence measurements**

Because one single method is never an accurate measure of adherence, the best approach utilizes multiple assessment techniques concurrently, as a way to improve the accuracy of adherence assessment [15,19]. However, the interpretation of the data may give problems. According to Dunbar-Jacob, combined measurements of adherence usually show poor relations between the various measures of adherence. The data suggest that different measures of compliance may not be comparable and, in addition, may have different relationships to clinical outcomes and to predictor variables [5]. Three examples will illustrate this:

- 1) Wagner et al assessed antiretroviral adherence [20]. They compared patient reported adherence to provider reported adherence and found that agreement between the two was based on chance ( $\kappa$  .07). However, patient report as well as provider reported adherence showed a consistent and largely *independent* association with clinical outcome (viral load). The authors suggest that patient and provider reported adherence independently measure actual adherence [20].
- 2) Concomitant use of pill count and self reported compliance showed that in most instances these two methods overestimated compliance compared with measurements of a digoxin marker (in oral gemfibrozil in patients with elevated cholesterol levels) [18].
- 3) Two studies conducted by the same group, one measuring adherence by self-report and the other by canister weight, produced strikingly different outcomes; self-reported adherence improved dramatically, whereas canister weight adherence evaluations revealed no difference between education interventions and control group [32]. Perhaps patients had overreported their adherence. Schmier, however, also found a number of patients who had underreported their adherence compared to canister weights [15].

With respect to the difference between self-reported adherence to dietary regimen and weight loss, Brown remarks “it may be that self report measures are not accurate indicators of compliance, producing inflated effect sizes. It must be noted however, that physiologic measures (weight loss) are not the best measures of compliance; and, consequently the disparate values for weight and self-reported dietary compliance may not necessarily be contradictory” [39].

Over time, the use of multiple indicators in empirical settings will assist in the determination of the best single evaluation method and the extent to which the method over- or underestimates adherence rates [15].

### 3. Conclusions and final remarks

This supplement has given an overview of the pros and cons of the various measurement tools and methods to assess patients' adherence to medical treatment. A distinction has been made between five categories of assessment methods a) direct observable behavior, b) subjective self-reports, c) objective monitoring of medication usage, d) objective physiological or biomedical measures, and e) health outcomes. The reviews reported in this supplement showed an obvious correspondence in the evaluations of the various assessment tools. It appears that, in general, the reviewers very often agree about the pros and cons connected to every measurement tool.

#### 1) A golden standard does not exist

Our first conclusion must be that a golden standard to measure adherence does not exist. Every method has its limitations. However, most authors agree that Electronic Monitoring (EM) devices are objective and accurate methods to assess adherence. And that some physiological or biochemical measures can be as adequate as well. Such objective measures are of particular importance in clinical trials, to assess the pharmacological actions and therapeutic dosages. According to Haynes, objective measures of adherence must be used whenever possible [29].

#### 2) The choice of adherence measure depends on its purpose

The second conclusion is that the choice of adherence measure depends on its purpose. No method of measuring compliance is applicable in all settings [13,25]. The more accurate methods are relatively costly and infrequently used in research setting and nearly non-existent in the clinical setting [31]. The choice of an adherence assessment tool should depend on its purpose: is it the individual patient in daily practice, the clinical trial, or epidemiological population surveys. In addition, the application of the tools remains a decision to be made on the basis of cost, ease of administration, the details and accuracy of the information requirements [5].

#### 3) In clinical practice improved interview methods seem promising

In daily clinical practice interviewing the patient is the most common method to assess patient adherence. Other ways of assessing adherence are not practical in most clinical settings [6]. Although patients' self-reports often may overestimate adherence, it is not necessarily so. Patients are willing to give accurate insight in their (non)adherence behavior if adequate interview techniques are used. A number of reviewers recommend new interview methods to facilitate an open discussion about patients' adherence [6,9,11,21]. The effects of these techniques are to be assessed and subsequently such techniques should be incorporated in medical education.

#### 4) A disappointing relation between adherence and health outcomes

It goes without saying that the ultimate aim of adherence is improved health outcomes for the patient. The results, however, indicate that the relation between adherence and health outcome is disappointingly low and sometimes even absent. This phenomenon is incomprehensible and puzzling. It may be clear that much research effort is needed to clarify the relation between adherence and health outcomes.

#### 5) How much adherence is enough?

Elaborating on the former conclusion, a serious problem is our lack of knowledge about the optimum extent of adherence to bring about the desired effects. How much compliance is enough? Different and sometimes disputable cut-off points are used in adherence studies. The following (unorthodox) approach has been suggested to increase our knowledge. According to Urquhart, ambulatory patients are of course free to take their medication as they choose, and they do so with a great deal of variety, without prior

ethical or regulatory approval [18]. This ubiquitous behavior of ambulatory patients creates a large, natural experiment in dose ranging. Although it frustrates the primary aims of prescribers or clinical investigators, it provides an important learning opportunity, because some of the patterns of administration employed by patients could never ethically be imposed by design in a clinical trial, yet may reveal salient illustrations of the pharmacodynamic properties of the drug and the consequences of various adherence behaviors [18].

#### **6) Adherence to be put in perspective in cases of self-management**

The importance of an accurate assessment of adherence may diminish in cases of self-management, but the reverse may also be true. Increasingly, patients are taught the self-management skills to deal with (chronic) diseases and regulate their own behavior. Nowadays, most drug regimes also allow for some flexibility and patient discretion in how and when the drugs are taken [21]. For example, patients with heart failure are increasingly trained to adjust their dose of diuretics in case of worsening symptoms (medication on an as-needed basis). This may influence the way compliance with diuretics can be measured and should be interpreted [23]. Besides, most life style changes and preventive practices require some degree of independent patient judgment and accommodation [21]. These degrees of freedom may complicate an adequate assessment of adherence. Future adherence measurements should be considered in the perspective of patients' self-management.

#### **7) In adherence assessment issues, the patient has been lost**

Finally, we have observed that patients' views on adherence assessment issues are virtually absent. That is why our final remarks concern the patient.

Firstly, patients can refuse treatment. The patient has a right to refuse treatment and this right must be respected [6]. In addition, patients are well-advised not to comply with irrationally prescribed agents, or with agents that are ineffective or downright toxic [18]. Studies often have ignored the possibility that, in some cases, non-adherence may be beneficial. This neglect is somewhat surprising considering that the rate of hospitalization of elderly persons attributable to adverse drug reactions is consistently higher than that attributable to non-adherence. The safety of medication use should have high priority in health care.

Secondly, it should be noticed that most assessments of adherence are dependent on the patients' willingness to disclosure information. Even electronic monitoring is dependent on the patient bringing back the pill bottle or monitoring devices [5]. So, most adherence assessments depend on patients' collaboration.

Thirdly, not all measures of adherence are equally acceptable to patients. Dunbar-Jacob found for example that 24% of patients refused to keep a diary and 23% of patients did not return the electronic monitor device for a variety of reasons [5]. Thus the acceptability of adherence measurement should be taken into account.

Our final recommendation is to involve patients and patients' points of view in issues of adherence assessments.

## 4. Overview of adherence measurement per review

### 23 reviews with significant differences between interventions

Authors	Diseases or disorder	Observations on measurement instruments	Recommendations on measurement instruments
Brown SA, 1990[39]	Diabetes (I and II)	1) Various measures of adherence 2) Comparing weight with self-reported dietary compliance, a large difference was found. 3) The disparate values for weight and self-reported dietary compliance may not necessarily be contradictory (see text)	1) Weight loss should not be used as a measure of dietary compliance. 2) Although compliance is difficult to measure, diaries, checklists, computer programs to monitor self-care activities, and other innovative methods are preferred. 3) Use reliable and valid instruments to measure patient outcomes.
Buring SM et al., 1999[40]	Peptic ulcer (H.pylori)	1) Dropouts 2) Discontinuation of therapy measured by the number of drop-outs.	--
Burke LE et al., 1997[31]	Cardiovascular	1) Various measures of adherence 2) An overview is given of adherence measurement methods (see table 2) for : - Pharmacological therapy - Exercise Therapy - Nutritional Therapy - Smoking Cessation - Multiple risk factors	1) Advances have been made in the measurement of compliance behavior. 2) More accurate measures are costly and seldom used in the clinical setting. 3) Improved methods of self-report as well as more available objective measures could facilitate the direct measurement of compliance.
Claxton AJ et al., 2001[30]	Various disorders	Electronic Monitoring devices (EM) as compliance measure.	EM devices could be used in clinical practice to evaluate the reason for lack of expected treatment effect.
Connor J et al., 2004[28]	Various disorders	Various (heterogeneous) measures of adherence and outcome.	Self-reporting and pill-counting may have resulted in overestimating of adherence, but it may have also contributed to underestimating of the effect of interventions.
Devine EC, 1996[41]	Asthma	Various measures of both self-reported adherence and provider-assessed compliance with therapeutic regimen.	--
Devine EC et al., 1995[42]	Hypertension	Various measures of medication compliance and compliance with appointments.	--
DiMatteo MR, 2004[43]	Various disorders	1) Various measures of adherence, divided in self-reported adherence and other measures of adherence. 2) Studies using self-reports of adherence yielded higher correlations than studies not using self-report	There is no evidence that the mean effect is a result of the use of self-reports of adherence at the aggregate level.

<b>Authors</b>	<b>Diseases or disorder</b>	<b>Observations on measurement instruments</b>	<b>Recommendations on measurement instruments</b>
Dodds F et al., 2000[27]	Psychotic disorders	1) Various measures of adherence 2) diverse definitions of compliance.	1) Subjective data on adherence may overestimate the success of the interventions, because they tend to be viewed as the least reliable. 2) However, measurement of plasma and urine levels also have difficulties (often depending on the half-life of the drug).
Dolder ChR et al., 2003[44]	Schizophrenia	1) Various measures of adherence 2) Three categories of adherence measurements: - direct measures (tracer substances etc.) - indirect measures (pill count, prescription refill etc.) - subjective measures (patient and others' reports).	1) All methods to measure adherence have their limitations and the variety of adherence measurement tools reflect the lack of a 'gold standard'. 2) Until there is a 'gold standard' for measuring adherence, multiple measures should be used when possible.
Giuffrida A et al., 1997[25]	Various disorders	1) Attendance/drop outs. 2) Compliance was measured as the proportion of patients who attended, divided by the proportion who did not attend. 3) Compliance identified as attendance is highly visible.	No method of measuring compliance with appointments or medication is applicable in all settings, thus assessing non-compliance is not easy.
Haynes RB et al., 2005[29]	Various disorders	1) Various measures of adherence 2) Most of the measures of adherence were imprecise, often relying on self-report: a method that was known to overestimate adherence and that could easily blur any differences between groups.	If adherence research is to advance, objective measures must be used whenever possible.
Iskedjian M et al., 2002[45]	Hypertension	1) Various measures of adherence 2) The included studies must have used the same instrument to measure adherence in each comparison group (experimental and control groups).	Further meta-analyses that include additional head-to-head comparative trials would be necessary to establish any differences between adherence rates for twice-daily and multiple daily regimen.
Macharia WM et al., 1992[26]	Various disorders	1) Attendance 2) Adherence to appointments was calculated as the proportion of patients who attended divided by the proportion who did not attend.	Monitoring attendance at appointments is clearly an adequate way of measuring compliance to supervised administration of care. It is not an accurate method for measuring compliance with self-administered (nonsupervised) medications or tests.

<b>Authors</b>	<b>Diseases or disorder</b>	<b>Observations on measurement instruments</b>	<b>Recommendations on measurement instruments</b>
Morrison A et al., 2000[34]	Hypertension	1) Various measures of adherence 2) The methods used to measure adherence were urine sampling, pill counting, self-report, MEMS and prescription refills. 3) The adherence rate was defined as the proportion of prescribed doses taken.	1) Self-report is of dubious reliability. 2) MEMS is an objective and reliable method of measuring vial opening, but it is an indirect measuring adherence. 3) Diastolic blood pressure is an objective and reliable endpoint.
Mullen PD et al., 1992[46]	Cardiac care	1) Various measures of adherence 2) When multiple outcomes were measured, the more objective measure was used.	A limitation of the meta-review are the different types of outcomes in the studies. Separate outcomes could not be combined.
Newell SA et al., 2000[3]	Cardiovascular	Various measures of adherence	1) Disappointingly, the studies showed a heavy reliance on subjective outcome measures as self-reports. 2) Employ direct, objective measures wherever possible and if not possible, employ multiple outcome measures or assess the validity of the measure in a subgroup of patients.
Richter A et al., 2003[47]	Various disorders	Adherence measures not reported.	No comments on adherence measures.
Roter DL et al., 1998[21]	Various disorders	1) Various measures of adherence 2) Five classes of compliance related assessments: a) Health outcomes (eg, blood pressure, hospitalization) b) Direct indicators (eg, urine and blood tracers, weight change) c) Indirect indicators (eg, pill count, refill records) d) Subjective report (eg, patients' or others' reports) e) Utilization (appointment making or keeping, and use of preventive services).	Compliance studies vary significantly. Definitions of interventions success vary from outcome-oriented markers of compliance (eg, health outcome or tracer substances) to process-oriented assessments (eg, pill count, refill, utilization), to subjective perceptions (patient or physician reports) to cognition (knowledge). These indicators of compliance are not equivalent; the measures tap different dimensions of compliance and reflect varied levels of effort and commitment.
Schroeder K et al., 2004[48]	Hypertension	1) Various measures of adherence 2) Adherence was measured in different ways, including: - Self-report; - Direct questioning, - Pill counts - Medication event monitoring system (MEMS).	1) Many studies used unreliable methods of measuring adherence, such as self-report and pill counts. 2) It appears that electronic monitoring provides more objective and reliable results.
Van Eijken M et al., 2003[2]	Various disorders (elderly)	1) Various measures of adherence 2) Many studies used self-reports. 3) One study employed MEMS.	1) The studies (RCT's) had several weaknesses such as poor measurements. 2) Self-reporting is known to overestimate compliance. 3) MEMS is one of the more reliable of all indirect detection methods.

<b>Authors</b>	<b>Diseases or disorder</b>	<b>Observations on measurement instruments</b>	<b>Recommendations on measurement instruments</b>
Vergouwen ACM et al., 2003[49]	Depression	1) Various measures of adherence 2) One study used MEMS to check reliability of patient reported adherence.	More evidence is needed from well-designed randomized controlled trials.
Zygmunt A et al., 2002[50]	Schizophrenia	Various measures of adherence - Pill count - Clinician report - Self report - Clinic visits - Urine tests - Family report - Plasma level - Case report - Combined assessments	1) Substantial variability existed in the definition and measurement of non-adherence. 2) There are novel techniques to assess dosage deviations (MEMS, urine tests). 3) Objective measures may enhance the chance of detecting dosage deviations. 4) The greater accuracy of objective measures must be weighed against their higher costs and the risk of lowering study participation among patients of greatest interest. 5) With improved measurement various types of non-adherence could be defined (such as intentional versus accidental mistakes) and these categories could be used to assign patients to appropriate interventions.

## 15 Reviews without differences between interventions

Authors	Diseases or disorder	Observations on measurement instruments	Recommendations on measurement instruments
Bender B. et al., 2003[32]	Asthma	1) Various measures of adherence 2) Limitation in many studies is reliance on inadequate adherence measures. 3) Self-reports usually exaggerate adherence. 4) This might explain the discrepancy between (reported) adherence and outcome.	1) Identify inexpensive, reliable technology to measure adherence. 2) Include as outcomes not only adherence but also disease and focused outcomes and patient focused outcomes as quality of life.
Higgins N et al., 2004[37]	Various disorders (elderly)	1) Various measures of adherence 2) Adherence was measured by either tablet counts alone, patient interview alone, or combined both of these methods.	There was a lack of consensus as how adherence should be calculated. Each study devised their own idiosyncratic scoring system, ranging from dichotomous 'adherent' or 'non-adherent' to complex calculations of adherence.
Merinder LB, 2000[51]	Schizophrenia	Various measures of adherence and outcome.	Further methodologically homogeneous and better reported studies are needed.
Newell SA et al., 1999[52]	Cardiovascular	Various measures of adherence	1) Disappointingly, the studies showed a heavy reliance on indirect outcome measures such as pill counts and self-reports. 2) Employ direct, objective measures wherever possible and if not possible, employ multiple outcome measures or assess the used measure's validity in a subgroup of patients.
Nosé M et al., 2003[53]	Schizophrenia / Psychosis	Various measures of adherence - patient interview - case-note evaluation - rating scale - urine test.	The different methods of assessing adherence were grouped together in the meta-analysis. These differences might have been responsible for some heterogeneity observed in the meta-analysis.
Pampallona S et al., 2002[54]	Depression	1) Various measures of adherence - kept appointments - pill counts - blood plasma levels - treatment drop-out - composite index. 2) The majority of studies employed direct measures of drug intake via pill count.	Limitations of the review are the different measures of adherence in the studies.
Peterson AM et al., 2003[55]	Hyperlipidemia	Refill and pill counts as measures of adherence.	More randomized controlled trials are needed.
Peterson AM et al., 2003[56]	Various disorders	1) Various measures of adherence 2) Adherence was measured by patient report, pill count, or medication profile.	1) Because of the lack of consistency in definitions and measurements, it was difficult to compare the merits of the studies. 2) A standard definitions and a standard measure of adherence are needed.



<b>Authors</b>	<b>Diseases or disorder</b>	<b>Observations on measurement instruments</b>	<b>Recommendations on measurement instruments</b>
Schedlbauer A et al., 2004[1]	Hyperlipidemia	1) Various measures of adherence - Self report - Prescription refill - Pill count. 2) Counting pills is vulnerable to manipulation, thus one author visited patient homes unexpected, for surprise pill counts.	1) The lack of a gold standard method of measuring adherence is one major barrier in adherence research. 2) More reliable data might be achieved by newer methods of measurement and more consistency in adherence assessment.
Sharp J et al., 2005[57]	Hemodialysis	1) Weight as measure of adherence (interdialytic weight gain (IWG))	Interdialytic weight gain (IWG) has been described as a valid assessment of adherence to fluid-intake restrictions.
Takiya LN et al., 2004[58]	Hypertension	Various measures of adherence	More randomized comparative trials are necessary.
Van Dam HA et al., 2003[59]	Diabetes	Various measures of adherence and outcome, e.g., - Patient behaviors - Patient biomedical issues - Patient functional measures - Psychological measures	More well designed intervention studies are needed.
Van derWal MHL et al., 2005[23]	Cardiovascular	Various measures of adherence (with medication, diet, weight, exercises etc.)	1) All adherence assessments have some limitations. 2) In many studies, the questionnaires that are used to measure compliance are not validated. 3) There are two questionnaires with content validity: The Heart Failure Self Care Behavior Scale; and, the Compliance Questionnaire. 4) A major challenge is to develop valid and reliable instruments to measure compliance.
Vermeire E et al., 2005[24]	Diabetes	Various measures of adherence	1) Each of the methods to assess compliance has drawbacks. 2) The lack of a valid method for measuring compliance has itself been a major barrier to compliance research. 3) Mostly adherence is assessed indirectly, leaving the reader with the question how valid this research was. 4) Adherence should be defined explicitly and the measurement instruments should be as direct as possible.
Yildiz A et al., 2004[60]	Depression	Drop-outs (or completers) as adherence measure.	--

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**Invitation of International Experts**







DIR552.05/COM-008/313.05/ES/HB +31 30 2 729 680 13 December 2005

**Subject: Invitation to participate in an international Expert Forum discussion on patient adherence**

Dear.....,

### **Invitation**

We have decided to approach you because of your excellent review on patient adherence to medical treatment. Currently we are finalizing a 'meta-review' on patient adherence. Your review is one of the 38 reviews – published between 1990-2005 – included in our meta-analysis. We wish to share our findings with all review authors.

The preliminary results of our meta-review indicate new directions in the theory and practice of adherence research. These new directions can only come into force when there is a sufficient support basis for them among the stakeholders in the field.

That is why we present these new insights for discussion to a selected panel of international adherence experts. The aim is to draw up a consensus statement on patient adherence. We greatly would appreciate your expert opinion in this matter. We invite you to participate in an Expert Forum discussion. The discussion will be conducted via a private closed-circuit website.

### **Introduction**

Let me introduce myself. I am director of NIVEL (the Netherlands Institute of Health Services Research) and professor of Health Psychology at the Utrecht University. My research focuses on patient adherence and doctor-patient communication ([www.nivel.nl](http://www.nivel.nl)). Our current research project is a collaboration with the departments of Pharmaceutical Sciences and of Health Psychology of Utrecht University. The parties involved in this research project are named in the document enclosed. Our research is independent without conflicts of interest (funded by the Netherlands Organization of Scientific Research).

### **The problem**

Non-adherence is a resistant problem. Effective and clinically relevant adherence interventions hardly exist. As we all know, a main problem in adherence research is the poor theoretical foundation of most adherence interventions. Besides, current adherence theories seem insufficiently powerful for significant improvements in patient adherence. New directions in adherence theory and practice are needed.



### **Aim of our meta-review**

That is why the aim of our meta-review is to discover which theoretical constructs may be potentially useful to be developed further. To this end, in this meta-review project three steps have been followed. Firstly, on the basis of the 38 included reviews, relatively effective or promising adherence interventions have been identified. Secondly, from these relatively effective adherence interventions we deduced the underlying theoretical perspectives and we formulated tentative conclusions. Thirdly, to explore the support base for these conclusions, a selected panel of international adherence experts – the Expert Forum - is now being invited to react to these tentative conclusions.

### **What do we ask from you?**

We kindly ask you to participate in this Expert Forum and react to our preliminary conclusions, summarized in 6 concise statements. As a member of this Expert Forum you will be asked to react to two questions:

1. Do you agree (or disagree) with the 6 conclusions derived from the meta-review, and why?
2. At the end of the forum discussion you will be asked in a separate mailing which conclusions deserve priority in future adherence research and practice. We will ask you to prioritize the 6 conclusions.

Your reactions may be brief or elaborate; that is entirely up to you. This discussion will be conducted via a private confidential website at the internet, exclusively accessible to members of the Expert Forum. It is planned to conduct the internet discussion in the first two weeks of February 2006. During this period, you may log in at any time that suits you. An interesting and fruitful discussion is to be expected.

### **What is in it for you?**

You will become a member of the international Expert Forum on patient adherence. With your permission, your opinions will be recorded in our research report. Your name as adherence expert will be printed on the first page of the report, together with the other participating forum members. You will receive the final report in print.

### **How to proceed?**

Following this letter of notification, we will ask by e-mail if you are willing to participate in this Expert Forum. After receiving your (e-mailed) confirmation, we will send you our meta-review report (draft) in print. The tentative conclusions – formulated as propositions – will also be published (in February) on the forum website, together with necessary details. You will receive a private login number giving access to the forum website. This enables you to get involved in the forum discussion.

### **E-mail address**

Preferably, we will send further information and details by e-mail. Would you please be so kind as to send your e-mail address to: *s.vandulmen@nivel.nl* (for reasons of planning please within one week).



Thank you very much in advance.

I would greatly appreciate your participation in our forum discussion and I look forward to your reply.

Yours sincerely,

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Enclosures:

- 1 Research team
- 2 Invited Forum of Adherence Experts



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## **Annex 8**

### **Procedure of the International Expert Forum Discussion**



## Procedure of the International Expert Forum Discussion

### Introduction

This appendix reports the steps that were taken to realise a forum discussion of international adherence experts. The aim was to discuss the preliminary results of our meta-review on patient adherence. The discussion was conducted via a special closed-circuit website, only accessible to the members of the expert forum via a private log-in number. Because this is a rather new method to gather expert opinions, we asked for the participants' experiences with this web-based forum discussion afterwards. This evaluation will also be reported in this appendix.

### Selection of experts and respondents

A total of 38 reviews were selected for our meta review. We invited all the corresponding authors of these reviews to participate in the forum discussion. A total of 35 authors were invited to participate (three authors were corresponding author of two included reviews). Initially, 25 experts (71%) indicated their willingness to participate in the forum discussion and of these, 20 (80%) actually did (see table 1). These participants received our meta-review report (draft) in print.

A few weeks after the closure of the forum, all participants were approached again to complete a short web-based evaluation questionnaire; 17 of them (response 85%) completed the questionnaire.

Table 1 Participants in the Expert Forum Discussion

Barbui, C.	Haskard, K.	Van Dam, H.A.
Bender, B.G.	Haynes, R.B.	Van der Wal, M.H.L.
Byrne, N.	Iskedjian, M.	Van Eijken, M.
Connor, J.	Merinder, L.B.	Vergouwen, A.C.M.
Devine, E.C.	Roter, D.L.	Vermeire, E.
DiMatteo, M.R. *)	Schroeder, K.	Wild, M.
Giuffrida, A.	Takiya, L.N.	Yildiz, A.

\*) M.R.DiMatteo acted as supervisor of K.Haskard

### Invitational letter

The experts were invited by Prof.Dr.Jozien Bensing, head of the research team. In the invitational letter was announced that "the preliminary results of our meta-review indicated new directions in the theory and practice of adherence research. These new directions could only come into force when there is a sufficient support basis for them among the stakeholders in the field". That was a main reason to present our tentative conclusions - formulated as six propositions - to an expert forum to ask their comments and opinions.

The experts were asked to react to three questions:

1. Do you agree (or disagree) with the six propositions derived from our meta-review, and why?
2. Can you prioritize the six conclusions at the end of the forum-discussion?
3. Would you complete an evaluation form at the end of the forum discussion?

In return, the participants' names would be printed at the front page of the research report.

The aim also was to draw up a consensus statement on patient adherence conjointly.

## Procedures

The following procedures with respect to the forum discussion were followed.

- a closed circuit forum website was developed by NIVEL and login numbers prepared.
- the six conclusions were published on this forum website (see Chapter 5).
- during four weeks the members could login at any moment (7x24).
- each of the experts saw and could react to previous reactions of other experts.
- after closure, we compiled a summary of the web-based discussion.
- the summary was sent back to the members for authorization.
- the next question to the members was to prioritize the six conclusions.
- finally, the forum members were asked to complete an evaluation form.
- (the members will receive this report in print).

## Summary of the forum discussion

At NIVEL, a summary of the forum discussion was compiled. In this summary careful attention has been given to the argumentations of each of the experts and all the pros and cons brought up by the experts.

This summary of the forum discussion was sent back (by e-mail) to the forum members for authorization. All forum members were in agreement with the summary.

The authorized summary is reported as Chapter six in this report.

## Prioritizing the conclusions

The questionnaire asked the experts to prioritize the six conclusions on the future of research and theory development in patient adherence which were also used in the forum discussion. Table 2 shows the results.

Table 2 Future directions in the area of patient adherence listed from highest to lowest priority

Meta-review conclusions	Mean (sd) assigned rank number*	Number (%) of experts assigning 1-3	Number of experts assigning 4-6
1 Future interventions: Explore simple interventions workable and feasible in (busy) clinical practice	2.7 (1.2)	13 (76)	4 (24)
2 Future theory development: Explore new directions by conjoint knowledge of medical, pharmaceutical, social and technical sciences	3.29 (1.8)	10 (59)	7 (41)
3 Future research: Explore the usefulness of patient participation in the development of (new) interventions	3.35 (1.5)	9 (53)	8 (47)
4 Future research: Identify non-adherent patients and apply interventions to this group specifically	3.35 (1.9)	8 (47)	9 (53)
5 Future theory development: Focus on improving adherence	3.65 (1.8)	6 (35)	11 (65)
6 Future research: Explore interventions directed at changing situational factors in adherence	4.5 (1.5)	5 (29)	12 (71)

\* range 1 - 6; 1 indicating highest priority, 6 lowest priority

## **Evaluation**

For reasons of evaluation, the experts were asked (by e-mail) to complete six questions about the use of the Internet Forum as a tool to obtain expert opinions.

On the question “How often did you access the website to participate in the internet forum discussion” most experts (76%) indicated that they did so more than once. Twelve experts (71%) said that they reacted on the comments put forward by other forum members in one or two of the six conclusions, four experts (24%) did not react on others at all and one said to have reacted on other experts’ comments in most of the conclusions.

Although the internet forum invited most of the experts to participate in the discussion, a real interaction may have to be stimulated somewhat more. As one of the experts remarked on the open question at the end in which experts were asked for comments that could help us in planning future web-based discussions: “I don't think that they can replace face-to-face discussions - but useful for gathering information for future discussions”. Another respondent said “I think it would be useful to explore ways to obtain more interaction among participants. A different structure of the discussion could improve the interaction and exchange of opinions among participants”. Someone else “...wondered why there was not a real discussion” and argued that “for me personally it took also some time to really participate and at that time many of my arguments were already written down, making it harder for me to react”.

When asked how people experienced the use of the web-based discussion as a way to dig up international expert opinions, 14 of them (82%) replied that it was better than using an individual written format, one said it was better than face-to-face discussions, while two disagreed on the latter. An answer on the open question revealed another asset of the internet forum, as being “...an economic way of exchanging views on a subject in search of consensus”.

Next, the experts were asked how they had experienced the amount of time (4 weeks) to enter their comments on the internet forum. Fifteen respondents (88%) answered that it was enough, one considered four weeks “too short” and one “too long”. One of the people who experienced the four weeks as being long enough, further on reacted: “It was good that the time to react on the forum was extended. Perhaps if it was longer people would have reacted more (I do not know if it works but if the panel receives an email if someone has responded on a conclusion they will notice the continuity of the discussion, but of course if they get reminders all the time it is not helpful). Also the conclusions were perhaps not that provocative and often in congruence with the opinions of the expert panel”. Most conclusions actually generated a considerable spread in answers of people either agreeing or disagreeing with a certain conclusion (see Chapter 5 of this report).

Finally, the experts were asked how they valued the instructions on the website. Fifteen of them (88%) responded that the instructions were clear and understandable and two indicated that it needs some improvement.

Two final remarks revealed that the experts were quite satisfied about the whole project by remarking: “I found this a useful and enjoyable experience” and “I felt the organisation of this forum discussion was very good and professional”.

