

A meta-analysis of the association between adherence to drug therapy and mortality

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Abstract

Objective To evaluate the relation between adherence to drug therapy, including placebo, and mortality.

Design Meta-analysis of observational studies.

Data sources Electronic databases, contact with investigators, and textbooks and reviews on adherence.

Review methods Predefined criteria were used to select studies reporting mortality among participants with good and poor adherence to drug therapy. Data were extracted for disease, drug therapy groups, methods for measurement of adherence rate, definition for good adherence, and mortality.

Results Data were available from 21 studies (46 847 participants), including eight studies with placebo arms (19 633 participants). Compared with poor adherence, good adherence was associated with lower mortality (odds ratio 0.56, 95% confidence interval 0.50 to 0.63). Good adherence to placebo was associated with lower mortality (0.56, 0.43 to 0.74), as was good adherence to beneficial drug therapy (0.55, 0.49 to 0.62). Good adherence to harmful drug therapy was associated with increased mortality (2.90, 1.04 to 8.11).

Conclusion Good adherence to drug therapy is associated with positive health outcomes. Moreover, the observed association between good adherence to placebo and mortality supports the existence of the “healthy adherer” effect, whereby adherence to drug therapy may be a surrogate marker for overall healthy behaviour.

Introduction

Poor adherence to drug therapy is considered a critical barrier to treatment success and remains one of the leading challenges to healthcare professionals.¹ Much of the literature on adherence focuses on methods for measuring adherence and identification of risk factors for poor adherence,²⁻⁵ with the premise that good adherence must be associated with good health outcomes.⁶ Individual studies have reported that good adherence to prescribed drugs (even placebo) was associated with a lower risk of mortality.^{w1-w3} This is contrary to the proposition that placebo has little effect on health outcomes⁷ and has led to speculation that adherence to drug therapy may act as an identifiable

marker for overall healthy behaviour, the so called healthy adherer effect.^{w1-w4 7-9} We tested this hypothesis by summarising studies of the relation between adherence to drug therapy and mortality, particularly in placebo arms.

Methods

Studies eligible for inclusion in our study were randomised controlled trials, retrospective analyses of data from randomised controlled trials, and observational studies evaluating the association between adherence to drug therapy and mortality.

A professional librarian (JV) carried out the literature search (see bmj.com). Two investigators (SHS, DTE) independently screened titles and abstracts to identify potentially relevant citations (see bmj.com for exclusion criteria). Each potentially relevant article was reviewed for the following inclusion criteria: described original research, explained the method used to measure adherence, provided a clear definition for good adherence, stratified patients into good and poor adherence groups, and reported mortality according to adherence groups.

Two investigators (DTE, RSP) used standardised forms to extract data from included articles (see bmj.com). We used the study authors’ definition to stratify participants into adherence groups. When the number of deaths according to adherence group was not specifically stated, we calculated this from available information. If information was insufficient to do this, we contacted the corresponding author.

Statistical analysis

We analysed data using Rev Man 4.2.7. Each arm in a randomised controlled trial was considered a discrete analysis of the relation between adherence and mortality. We used a random effects model to calculate pooled odds ratios and 95% confidence intervals.¹⁰ We used predetermined subgroups to identify potential sources of heterogeneity (see bmj.com).

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Results

In total, 5012 citations were excluded after review of the title and abstract (see bmj.com). From the 79 potentially relevant articles, 21 studies with 46 847 participants met the inclusion criteria.^{w1-w21} Eight were randomised, placebo controlled trials (37 701 participants) reporting mortality according to adherence group for each arm in a retrospective analysis.^{w1-w4 w8 w16-w18 w22} Thirteen cohort studies (9146 participants) reported mortality according to adherence groups.^{w5-w7 w9-w15 w19-w21} (See bmj.com for the characteristics of the included studies.) Eight studies evaluated drug therapy in participants with a recent myocardial infarction,^{w1-w8} seven were in patients infected with HIV,^{w9-w15} and two were in primary prevention of heart disease.^{w16 w17} The remaining studies were in patients with type 2 diabetes,^{w18 w22} hyperlipidaemia,^{w19} heart failure,^{w20} and immune suppression after heart transplant.^{w21} Fifteen studies reported a threshold to define good adherence.^{w1-w5 w7 w8 w11 w13-w19 w22} All cause mortality was the primary outcome in nine studies^{w2 w3 w9-w13 w15 w19} and a secondary outcome in 12.^{w1 w4 w5-w8 w14 w16-w18 w20-w22} One study reported arrhythmic mortality according to adherence group.^{w4} Data for all cause mortality were not available for this trial.^{w4 11}

The primary analysis of mortality risk according to adherence group was based on 2779 (5.9%) deaths in 46 847 participants. Overall, 1462 (4.7%) deaths occurred in 31 439 participants with good adherence to drug therapy and 1317 (8.5%) deaths in 15 408 participants with poor adherence. The pooled odds ratio for mortality for good compared with poor adherence was 0.56 (95% confidence interval 0.50 to 0.63). Some heterogeneity was found: Q statistic P=0.08, I²=28.6%.

The placebo arms from eight studies contained 19 633 participants and reported 996 (5.1%) deaths.^{w1-w4 w8 w16-w18 w22} Overall, good adherence to placebo was associated with a lower risk of mortality: pooled odds ratio 0.56, 0.43 to 0.74 (fig 1). Some heterogeneity of effect was found: Q statistic P=0.05, I²=51.2%. A subgroup analysis restricted to studies of drug therapy after myocardial infarction reduced variance substantially: Q statistic P=0.79, I²=0%,^{w1-w4 w8} The pooled odds ratio of these five studies was 0.45 (0.38 to 0.54).

In two studies active drug therapy increased the risk of mortality compared with placebo.^{w22 11} Therefore separate models were constructed to summarise the effect of adherence to active drug therapy found to be harmful compared with beneficial (fig 2). The two studies evaluating adherence to harmful drug therapy reported 53 (6.8%) deaths in 778 participants.^{w4 w18 w22} The pooled odds ratio for mortality was 2.90 (1.04 to 8.11) for participants with good adherence to the active treatment (fig 2).

The association between adherence to proved beneficial drug therapy and mortality was reported in 19 studies involving 26 436 participants and 1730 (6.5%) deaths.^{w1-w5 w5-w17 w19-w21} The pooled odds ratio from these studies was 0.55 (0.49 to 0.62) for mortality in participants with good adherence (fig 2). These observations were homogeneous (Q statistic P=0.71, I²=0%). Stratification by study characteristics did not result in substantive changes to these relations (see bmj.com).

Discussion

This meta-analysis of 21 studies, involving 46 847 participants, showed a consistent association between adherence to drug therapy and mortality. For participants with good adherence to placebo or beneficial drug therapy, the risk of mortality was about half that of participants with poor adherence. Conversely, the risk of mortality was more than doubled for participants with good adherence to proved harmful drug therapy compared with participants with poor adherence.

The association between adherence to harmful therapy and mortality is important in the light of recent issues of patient safety and post-marketing drug surveillance. Our observation suggests that stratification by adherence group may facilitate earlier identification of harmful therapies if the rate of adverse events is higher in participants with good adherence. According to the consolidated standards of reporting trials statement, investigators should, at a minimum, report the number of participants receiving the intended treatment.¹² Although randomised clinical trials will often measure adherence, this information is usually reported only as an overall adherence rate.¹³ An array

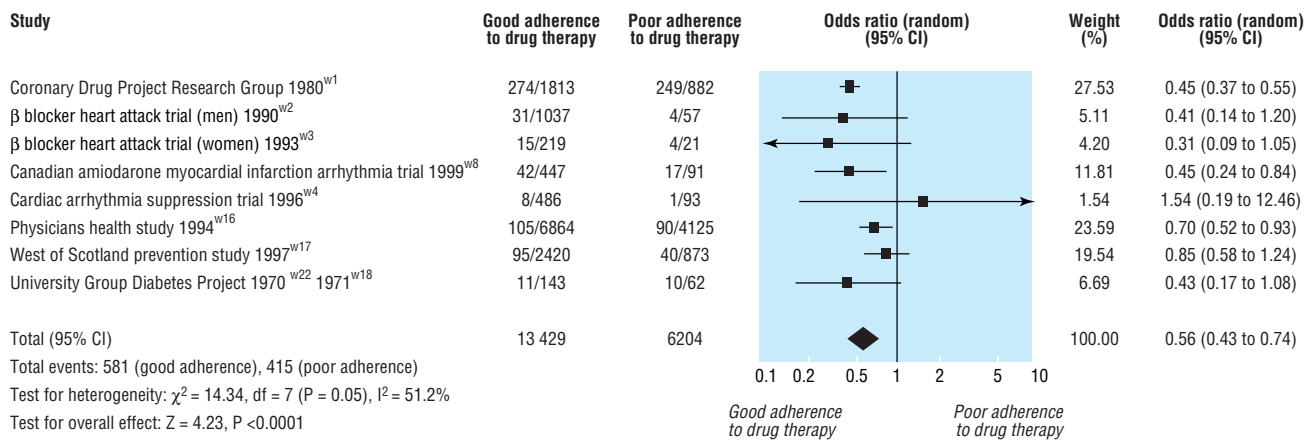


Fig 1 Association between adherence to placebo and mortality

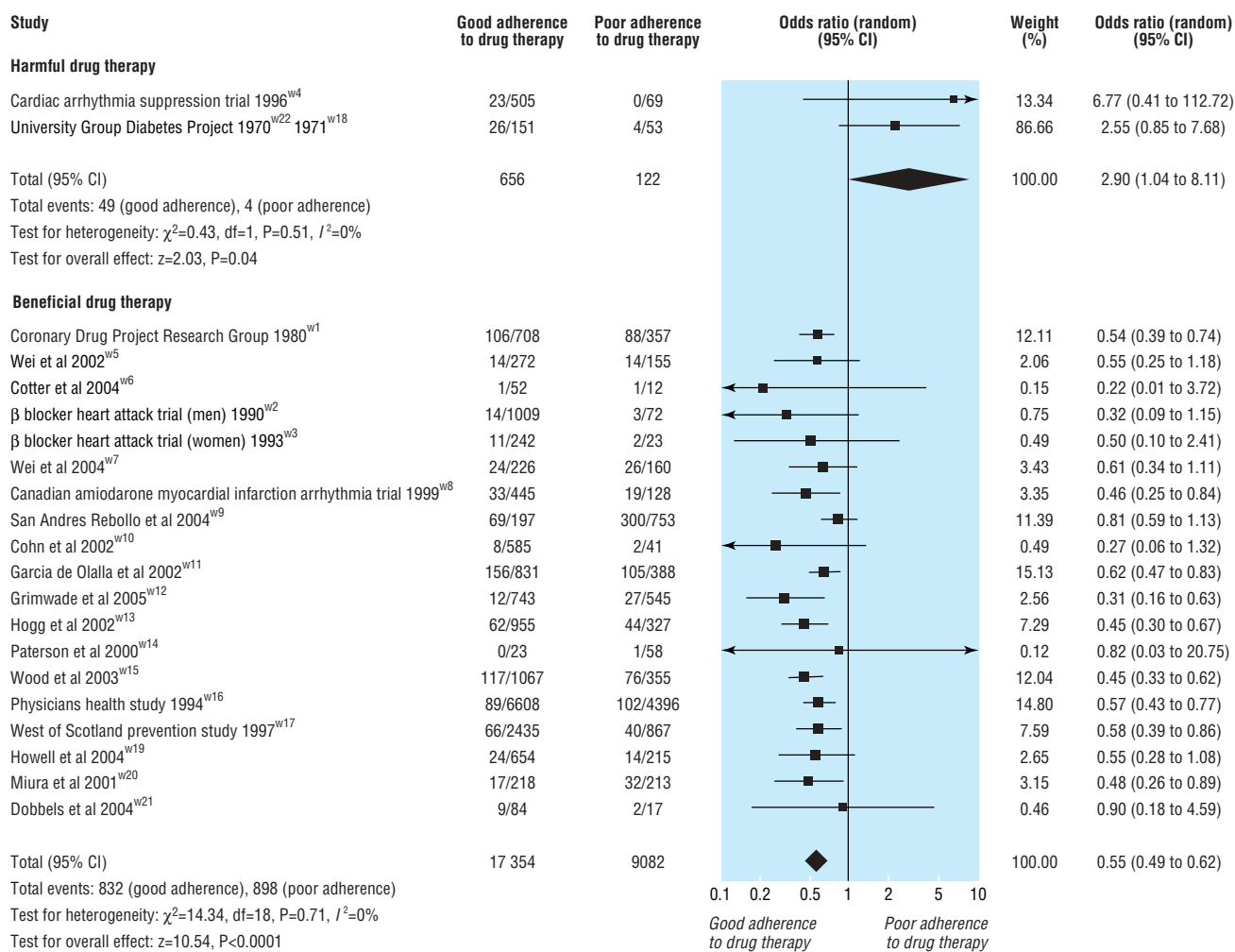


Fig 2 Association between adherence to harmful or beneficial drug therapy and mortality

of adherence rates can confound the association between treatment and response and substantially affect generalisability.¹³⁻¹⁵

One review on admission to hospital and mortality associated with cardiovascular disease found that seven of 12 studies had a significant association between adherence and outcomes and that adherence to placebo was associated with improved outcomes in three studies.⁸ More recently another study found that the risk of a poor health outcome was 26% lower in participants with good adherence.⁶ Although that meta-analysis included studies from a wide range of medical conditions, drug therapy was included with a variety of other healthcare interventions. In addition, the placebo arms from controlled trials were excluded from their analysis. Our study confirms, updates, and extends these observations by including studies from across several disease states and summarises the observations between adherence to drug therapy, including placebo, and mortality.

Our study shares limitations inherent with meta-analyses in general and with studies of adherence specifically. Firstly, although unlikely, studies relevant to the research question may have been missed. Secondly, our data sources were observational studies, thus restricting our ability to explore fully the influence of

unmeasured confounding variables. For example, participants with good adherence to study drugs (even placebo) may also have good adherence to other healthy behaviours,^{w1-w4 7-9} which could independently affect the risk of mortality. Conversely, participants with poor adherence may have consciously chosen to use a lower dosage^{16 17} or have other conditions, such as depression, that affect adherence.^{9 18} In the absence of individual patient data to control for these factors, we tested the healthy adherer effect hypothesis and assumed that the presence of good adherence is a marker for overall healthy behaviour.^{w1-w4 7-9} Thirdly, we observed a wide variety of measurement methods and definitions for good adherence. Grouping studies according to measurement method and definition for good adherence did not, however, result in substantive changes to our overall observation. Finally, with the exception of two studies,^{w6 w20} all studies used indirect methods to measure adherence. These methods are limited by the assumption that drug acquisition is a reasonable surrogate for consumption. This assumption would, however, overestimate exposure and bias our observation towards the null.

Our findings support the tenet that good adherence to drug therapy is associated with positive health outcomes. Moreover, the observed association

What is already known on this topic

About one in four people do not adhere well to prescribed drug therapy

Poor adherence is considered a critical barrier to treatment success and remains an important challenge to healthcare professionals

What this study adds

Good adherence to drug therapy is associated with positive health outcomes

The observed association between adherence to placebo and mortality supports the premise of a healthy adherer effect, where adherence to drug therapy may be a surrogate marker for overall healthy behaviour

between good adherence to placebo and lower mortality also supports the existence of the healthy adherer effect, whereby adherence to drug therapy may be a surrogate marker for overall healthy behaviour.

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Commentary: The healthy adherer and the placebo effect

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Simpson and colleagues report their systematic review's finding that good adherence to placebos as well as to drug treatments is associated with reduced mortality.¹ They hypothesise that this intriguing finding supports the concept of the "healthy adherer" effect, whereby adherence to drug treatment may be a surrogate marker for overall healthy behaviour.

The potential benefits of any new treatment regimen arise in the context of patients' powerful lifestyle habits and resources, as well as their health status and their histories of health behaviour. In addition, a patient brings to each brief meeting with a doctor their habits for drug adherence. It is quite possible, therefore, that people who adhere to healthy lifestyles also tend to take care of themselves by greater adherence to prescribed treatments.

Evidence on the placebo effect yields a complementary hypothesis, for the association between adherence to placebo and reduced mortality. Controlled trials have measured the positive effects of placebos on a range of physical outcomes for over half a century.² Barrett and colleagues argue that healing lies not in the treatment but rather in patients' emotional and cognitive processes of "feeling cared for" and "caring for oneself."³ The meanings people attach to

the "pill" and "behaviour of the healer" are the key to the mind-body connection leading to health outcomes.

The association with lower mortality in the paper by Simpson and colleagues could arise from positive interaction between these healthy adherer and placebo related effects. If true, what would these hypotheses imply for doctors' decisions and the encounters they have with patients? Traditionally, the healer's greatest tool has been to listen and build on the patient's story and its meaning to determine the most appropriate healing ceremonies, rituals, and therapies. Coupled with other patient centred approaches, practice based on these hypotheses could yield extra value in treatment regimens that patients agree to, believe in, and will sustain over time. Patients' adherence to treatments would show that they were caring for themselves while their clinical encounters would reinforce that their doctors were caring for them.

Motivational interviewing may also be useful.⁴ For example, asking a patient, "What would make it worth while for you to take this medication in the next month?" may elicit the patient's most serious fears, valued outcomes, or social pressures. These can be used to shape prescribing decisions, to frame an open and truthful discussion of the treatment rationale, and