

Evidence for compliance with long-term medication: a systematic review of randomised controlled trials.

Abstract

Background

Pharmacists play a pivotal role in optimising medication use which often includes actions to maximise compliance with long-term medication. The best evidence to support medication use is derived from randomised controlled trials (RCTs). It is often assumed that 100% compliance is required to obtain the outcomes identified in the trial. This assumption needs to be examined.

Objective

To systematically review the reporting of compliance in RCTs of long-term medications.

Method

RCTs published in the New England Journal of Medicine, Journal of the American Medical Association, Lancet and BMJ in 2012, were reviewed to identify trials of medications for long-term use in adults. These trials were examined to evaluate the reporting of compliance.

Main outcome measures

The proportion of trials reporting compliance data, the methods used, and the proportion of trials using more than one method to determine compliance.

Results

Of the 289 RCTs published in 2012, 25 assessed long-term medications in adults. Compliance was reported in 12 (48%) studies and only 2 (8%) studies used more than one method to measure compliance. Pill count was the most commonly reported method for measuring compliance, with patient reports and blood levels also being used.

Conclusion

The reporting of compliance in RCTs is poor and the methodology inconsistent. The methods used overestimate compliance. If compliance in a clinical trial is low, the evidence for the effectiveness and most importantly safety of the medication(s) is questionable. Two or more methods, one of which is standardised, should be used to measure compliance in clinical trials. The requirement to report compliance should be included in publication guidelines.

Impact of findings on practice

- Compliance is underreported and underestimated in randomised controlled trials, therefore estimates of the difference between efficacy and effectiveness need to be revised.

- Non-compliance in clinical trials can lead to overestimation of the effective dose and underestimation of the side effects, therefore pharmacists should consider the evidence before acting to maximise compliance.
- Standardised measures of compliance need to be developed and implemented so that adherence can be compared in different populations and situations.

Keywords (MeSH) – clinical trials, systematic reviews, medication adherence, chronic disease, pharmacoepidemiology

Introduction

The prevalence of chronic disease is increasing[1, 2]. Consequently, the use of medication to treat chronic conditions is also increasing[3, 4]. Ensuring optimal outcomes from medication is therefore a global priority in which pharmacists have a pivotal role. Patients need to take their medication in order for it to have an effect; therefore medication taking behaviour is important. The terminology however is less so. Epidemiologically it does not matter whether a patient is obedient (compliant), autonomous (adherent)[5] or collaborative (concordant), what matters is whether they take a dose. The term compliance has been chosen to represent the proportion of prescribed doses taken; other terminology is that used in the studies referenced.

Medication compliance in chronic conditions is less than that in acute conditions, with reports from clinical trials ranging between 43% and 78%[6]. Compliance may decrease over time, for example, about half of the patients prescribed an anti-hypertensive had stopped taking it within one year[7]. Because compliance is lower in chronic conditions, pharmacists tend to focus on improving the compliance of patients taking long-term medication. In Australia in recent years, pharmacists have been remunerated for clinical interventions to improve compliance, for example intervening with a patient who “chooses to take a medicine PRN instead of on a regular basis (when the latter was intended)”[8].

From a public health planning point of view it is important to be able to assess the safety and efficacy of medications[9], in the populations that will be taking these medications. Safety and efficacy are closely linked with and usually depend upon compliance. The highest level of evidence for safety and efficacy comes from randomised controlled trials, yet the reporting of compliance in clinical trials is poor, identifying a serious defect in the quality of the evidence. Souter and Kennedy reported that only 19% (61/324) of clinical trials published in the Lancet and BMJ between 1969 and 1972 reported compliance, with only 2% (6/324) using more than one method to assess compliance[10]. More than two decades later, in 1997-1999, Jayaraman et. al. reported that this had increased to 47% (78/165) with 16% of trials using more than one method of assessment[11]. In 2003, the WHO recommended, “A multi-method approach that combines feasible self-reporting and reasonable objective measures in measurement of adherence behaviour”[9]. Because there are serious defects in the reporting of compliance in clinical trials, and with the increasing emphasis placed on medication compliance in chronic conditions, the aim of this study was to assess the

reporting of compliance in randomised controlled trials (published in 2012) of medications for long-term use in non-institutionalised adults.

Method

The four highest ranked medical journals based on citations in Web of Science (Thomson Reuters), i.e. The New England Journal of Medicine (NEJM), The Journal of the American Medical Association (JAMA), The Lancet and the BMJ, were chosen for this systematic review. It was expected that the highest ranked journals would have the highest quality standards and therefore that the articles published in them would be the most likely to contain information on patient compliance. The Lancet and BMJ have been used in previous studies[10, 11].

Randomised controlled trials (RCTs) published in these journals in 2012 were identified using Ovid Medline (search term: journal name, limits: publication types - *randomized controlled trial*, and publication year - 2012). Titles and abstracts were manually searched to identify parallel design trials comparing medicines. The full text of these articles was then manually searched to identify studies that compared single named medicines or fixed dose combinations in a single dose unit (e.g. tablet or capsule), taken by mouth at least once or more a day, for a minimum of one month.

Exclusion criteria were chosen to maximise the clarity of our findings by limiting the background variation (noise) and confounding factors. Previous research has identified that the medication, dose form[12], route[13], complexity of the regimen[3, 6, 13, 14] and duration of treatment[7] can influence compliance and are therefore likely to add to background variation. Combinations of medicines where each drug needed to be taken as a separate tablet were therefore excluded. As were trials where the medicine was not administered by the most common route, i.e. orally; or if the dose frequency, number of tablets, or duration (within the trial) varied. Comparisons with 'best available therapy' if the medication was not named were also excluded as it was not possible to determine whether the other exclusion criteria applied or not.

Trials including children or those in institutions were excluded, as it was likely that these patients did not have either: personal responsibility for, or control over, their compliance.

Study descriptions and compliance data including the method of measuring compliance and the reported rate/s of compliance from the remaining articles were tabulated.

Results

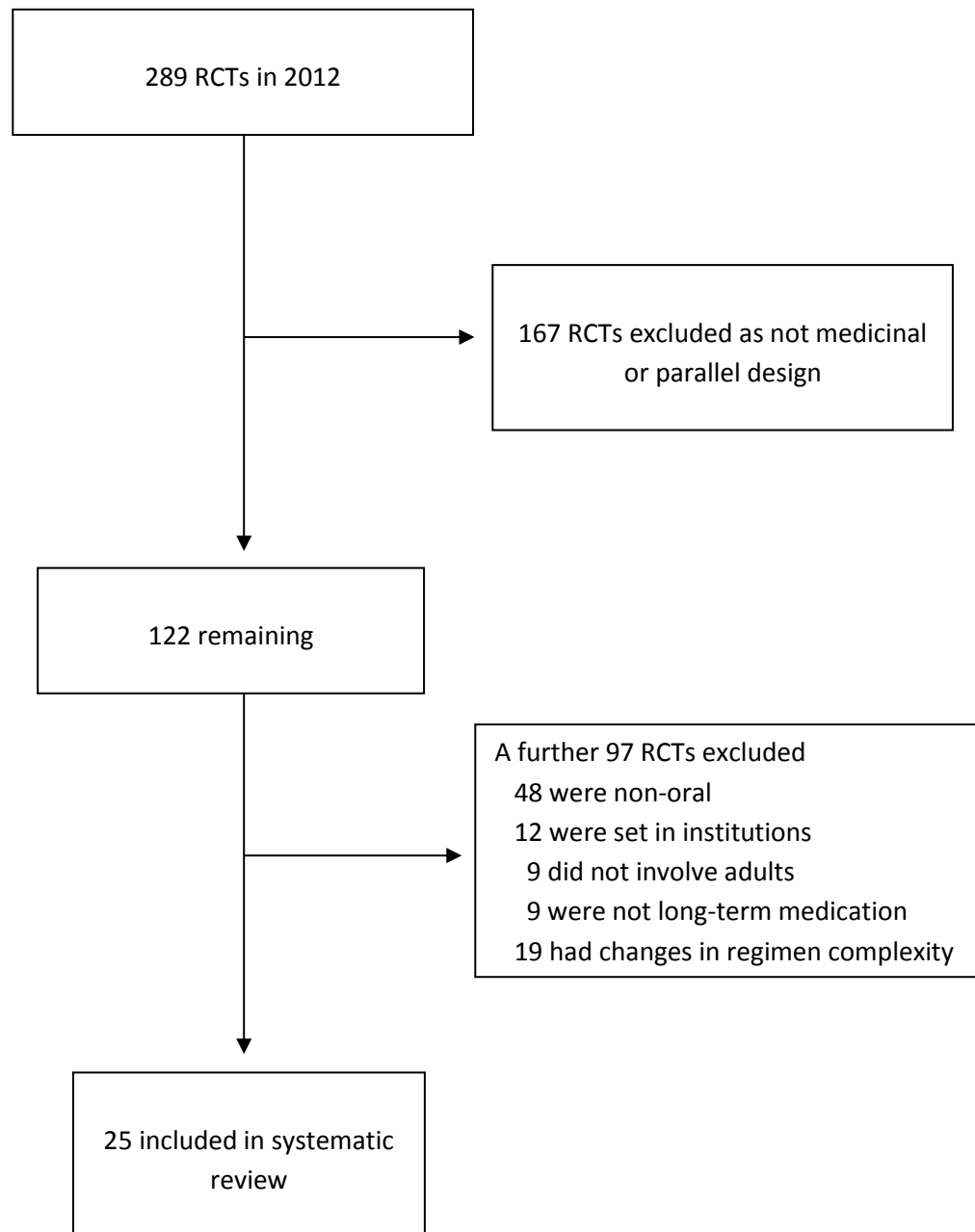


Figure 1 Selection process for systematic review

Of the 289 RCTs published in the NEJM, JAMA, Lancet and BMJ in 2012, only 122 were parallel comparisons of medicines (or medicine and placebo); 97 of these were eliminated based on the exclusion criteria, leaving 25 for inclusion in the systematic review (Fig 1). Of these articles 15 were from NEJM, 5 from JAMA, 5 from The Lancet and 0 were from the BMJ. Compliance was reported in

12 (48%) studies (Table 1). (The study that used the proportion of patients in the treatment group discontinuing and proportion of patients in the placebo group commencing treatment as a measure of non-adherence was not counted as this 'adherence' was to the randomisation protocol rather than the study medication.) The method for detecting or assessing compliance was missing in 16 (64%) studies. Of the studies that reported the detection method, three studies (12%) used pill counts, two (8%) used patient report, and one (4%) used blood/cell concentration. Only 2 (8%) studies, both focussing on HIV, used all three methods. The poor reporting of the detection methods, the variety of methods used, and the associated lack of a common denominator, prevented the calculation of an overall mean or range for compliance, for example, pill counts comparing the number of doses actually taken with the number that should have been taken cannot be compared with pill counts reporting the percentage of people taking between 80% and 120% of doses.

(Place table 1 here)

Discussion

The reporting of compliance in clinical trials for long-term medications is poor, with less than half of the trials including compliance data, and many of these failing to identify the measurement method used. In contrast to the NEJM and The Lancet all but one of the articles published in JAMA included the method of detection and compliance data. No trial published in the BMJ met our inclusion criteria.

The inclusion of one standardised method of measuring compliance in all trials would greatly improve comparisons across treatments and clinical trials. Little has changed since 2005 when Jayaraman et.al. noted that the reporting of compliance occurred in only 47% of clinical trials[11]. Despite WHO recommendations that two or more methods should be used to assess compliance[9], only 2 studies did this and both were assessing treatments for HIV where a high level of compliance is required to suppress the virus.[15] The recent publication of guidance for protocols of clinical trials[16], which recommends that procedures for monitoring adherence be included in trial protocols, may improve this situation in the future, however the reporting requirements for clinical trials, i.e. CONSORT guidelines[17], should be updated to reflect the importance of the publication of adherence data.

The variety of compliance measures used reflects methodological difficulties and raises some quality issues. The ideal method(s) of measuring compliance would be accurate, easy to perform, inexpensive and provide information on the number of doses taken, the correct timing of those doses and reasons for omitting or increasing doses. The most popular methods, i.e. pill count, patient report, drug (or marker) levels, and electronic monitoring, provide different, though complimentary, information on compliance. Each has its own pros and cons, but most overestimate compliance. Pill count is easy to perform and inexpensive[18], however it provides no information on the timing of doses and can be affected by lost pills or patients retaining or discarding pills instead of returning them[6, 18]. Up to 30% of clinical trial participants may discard study medications[19].

Patient report is inexpensive[18] and can provide additional data as to why patients take too little or too much of their medication, unfortunately while it is a specific measure, in that reports of poor compliance are accurate, it is not sensitive, as poor compliers may not admit to missing doses or taking them at the wrong time[5, 13, 19]. There are numerous instruments to capture patient self-reports but all fail to accurately assess or explore one or more important facets of compliance or non-compliance[20]. The ideal instrument would be responsive, i.e. able to detect clinically important changes in compliance, reliable, validated against non-questionnaire methods, be suitable for use by patients and carers, and provide information on the cause of non-compliance, including being able to distinguish between intentional and unintentional compliance[20].

Levels of a medication (or a marker) that can be measured in body fluids accurately reflect compliance if the medication is completely absorbed, has a long half-life and 100% is excreted unchanged[10]. Assessing the compliance of medicines with shorter half-lives is confounded by white coat adherence, i.e. when patients increase compliance before their appointment[21]. Obtaining body fluids may require invasive procedures and testing is often expensive[6].

The use of electronic monitoring is limited by its expense[6, 9]. It has been considered to be the gold standard as it provides information that includes the timing of the dose by recording when the medication container was opened[6]. Ideally the opening of the container reflects a patient taking a dose of the medicine; however the container may be opened without a dose being taken[6] or with more than the recommended dose being taken. No information is obtained as to the reasons for non-compliance. When fitted to pills, emerging technology, in the form of transmitters that can send consumption data to a wristwatch,[22] has the potential to become the new gold standard for assessing compliance.

The journals selected were the highest ranking, and the studies published in them assumed to be of the highest quality. It is likely that the reporting of compliance is higher in these publications than others. The exclusion criteria are both strengths and weaknesses of this study as while background variation has been limited, our results cannot be extrapolated to children, adults in institutions, or other routes of administration.

Pharmacists' interventions to improve compliance need a stronger evidence base in relation to the medicines targeted. Without compliance data there can be no true estimate of safety and efficacy[10]. If compliance is poor, efficacy may be underestimated. If poor compliance is compensated by the use of higher doses in clinical trials, there is the risk that after the medicine is marketed, those who are compliant have a higher risk of side-effects[19]. Medications considered to be safe have shown increased toxicity after patient education sessions, also, recommended doses have been reduced after marketing due to the identification of dose-related toxicity[19].

Perceived or genuine lack of benefit is a common cause of non-compliance[14, 23], paradoxically, compliance, even if it is with a placebo, has been shown to improve outcomes[24]. Common sense would indicate that a patient should not continue to take an ineffective medication however determining whether non-compliance or therapeutic failure is the cause is not straightforward.

The correct dose balances risk and benefit; too low a dose can result in therapeutic failure, too high a dose can result in side-effects. Interestingly, non-compliance has been shown to be an effective method of dose titration[25]. Research comparing both positive and negative outcomes from

medications in relation to dose and compliance in pre- and post-marketing studies is needed. Analysis by intention to treat (as randomised) may better reflect the real world use of a medication, however, complementing this with correlations of compliance and both effectiveness and side-effect data would assist clinical decision making.

Conclusion

The reporting of compliance in clinical trials is poor and would be improved by including a requirement to include compliance data in the CONSORT guidelines[17]. Ideally, trial results would relate compliance to benefit and adverse effects to provide a stronger evidence base for the use of medications. As recommended by the WHO[9] and SPIRIT [16], two or more methods of measuring compliance should be included in trial protocols and the reporting of trials. Based on feasibility and cost; pill count and patient report with an appropriately valid instrument would be first line, however other measures may be more suitable depending on the primary and secondary outcomes measured; population studied; and validity, reliability, feasibility and cost of the compliance measure.

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Table 1 Articles included in the systematic review

Reference	Condition	Treatment/Duration	Method	Compliance
NEJM				
Brighton et. al.[26]	Venous thromboembolism	aspirin 100mg or placebo, daily; duration range 2-4 years	Proportion of: aspirin patients <i>discontinuing</i> , and placebo patients <i>initiating</i> anticoagulants/antiplatelets	15% aspirin, 7%placebo, i.e. 22% overall, averaged over the study period
Comi et. al.[27]	Multiple sclerosis	laquinimod 0.6mg or placebo, once daily; duration 24 months	Not reported	Not reported
Donnez et. al. [28]	Fibroids	ulipristal acetate 5mg, 10mg or placebo, once daily; duration up to 13 weeks	Not reported	Not reported
McCarthy et. al.[29]	Multiple myeloma	lenalidomide 10mg (range, 5 - 15mg) or placebo, daily; median follow-up 18 months	Not reported	Not reported
Morrow et. al.[30]	Atherothrombotic events	vorapaxar 2.5mg or placebo, once daily; median follow-up 30 months	Not reported	Not reported
Parving et. al.[31]	Type 2 diabetes	initial dose alskiren 150mg (increased to 300mg at 4 weeks if no safety concerns) or placebo, once daily; median follow- up 32.9 months	Not reported	Not reported
Roe et. al.[32]	Acute coronary syndromes	loading dose prasugrel 30mg or clopidogrel 300mg; maintenance dose prasugrel 10mg (5mg if aged ≥ 75 years/ < 60 kg) or clopidogrel 75mg, daily; average duration 14.8 months	Not reported	Not reported
Sandborn et. al.[33]	Ulcerative colitis	tofacitinib 0.5mg, 3mg, 10mg or 15mg or placebo, twice daily; duration 8 weeks	Not reported	Not reported
Scher et.	Prostate cancer	enzalutamide 160mg (4 x 40mg	Not reported	Not reported

al.[34]		capsules) or matching placebo, once daily; median duration enzalutamide 8.3 months, placebo 3 months		
Verstovsek et. al.[35]	Myelofibrosis	ruxolitinib 15mg for a platelet count of 100×10^9 - 200×10^9 per litre, 20mg for a count $>200 \times 10^9$ per litre or placebo, twice daily; median follow-up 32 weeks	Not reported	Not reported
Ledermann et.al.[36]	Ovarian cancer	olaparib 400mg or placebo, twice daily; median duration olaparib 206.5 days, placebo 141 days	Not reported	Mean adherence 85% olaparib, 96% placebo
Mega et. al.[37]	Acute coronary syndrome	rivaroxaban 2.5mg, 5mg or placebo, twice daily; mean duration 13 months	Not reported	93.9% (2.5mg), 94.0% (5mg), & 94.6% (placebo) of patients were $\geq 85\%$ compliant
Schwartz et. al.[38]	Acute coronary syndrome	dalcetrapib 600mg or placebo, daily; median follow-up 31 months	Not reported	89% of patients in both groups had at least 80% adherence during the time they were receiving the study drug
Thigpen et. al.[39]	HIV	tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) or matching placebo, once daily; median follow-up 1.1 years	Monthly pill count; Self-report (preceding 3 days) Blood levels	84.1% TDF-FTC, 83.7% placebo; 94.4% TDF-FTC, 94.1% placebo Not presented
Van Damme et. al.[40]	HIV	TDF-FTC or placebo, once daily; Duration 52 drug weeks and 8 follow-up	Pill count Self-report Blood levels	Consistent with ingestion of study drug on 88% of days; 95% of participants usually or always took the drug; Revealed much lower levels of adherence
JAMA Thadhani et.al.[41]	Cardiac structure in patients with kidney disease	paricalcitol 2ug or matching placebo, daily; duration 48 weeks	Not reported	Not reported

Fried et. al.[42]	Liver disease in patients with Hepatitis C	silymarin 420mg (3 capsules of silymarin and 2 placebo), 700mg silymarin (5 capsules of silymarin) or placebo (5 capsules), three times daily duration 24 weeks	Dose counts (doses were presented in sealed cups adherence calculated as a percentage of the medication dose cups dispensed compared with cups returned at follow-up)	95% of participants met or exceeded an 80% threshold for adherence (95.2% silymarin 420-mg, 93.0% silymarin 700mg, 91.8% placebo)
Lok et. al.[43]	Cardiovascular events	fish oil (4 x 1g) or matching placebo, daily; duration 12 months	EPA incorporation into endogenous cells measured by gas-liquid chromatography	Adherence confirmed
Paton et. al.[44]	HIV	hydroxychloroquine 400mg (2 x 200mg tablets) or matching placebo, once daily duration 48 weeks	Self-report (questioned about changes to the study medication schedule, missed capsules in the previous 2 weeks, missed capsules since the previous visit, and any periods of treatment interruption)	>90%of prescribed doses taken by 81% of patients in the hydroxychloroquine group and 83% in the placebo group
Sesso et. al.[45]	Cardiovascular disease	multivitamin or placebo, daily; median follow-up 11.2 years	Self-report (annual questionnaire) Shown to be highly reliable in physicians, as taking at least two-thirds of the pills	76.8% multivitamin, 77.1% placebo at 4 years; 72.3% multivitamin, 70.7% placebo at 8 years; 67.5% multivitamin, 67.1% placebo at the end of follow-up
The Lancet Solomon et. al.[46]	Heart failure	Initially LCZ696 50mg or valsartan 40mg, twice daily, titrated to LCZ696 200mg or valsartan 160mg, twice daily over 2-4 weeks duration 12-week main study period and 24-week extension	Not reported	Not reported
van der Graaf et. al. [47]	Soft-tissue sarcoma	pazopanib 800mg or placebo, once daily with no cross-over; median duration pazopanib 4.6 months, placebo 1.6 months	Not reported	Not reported
Burant et.	Type 2 diabetes	TAK-875 (6.25, 25, 50, 100 or 200mg)	Not reported	98% to 100%

al.[48]		or glimepiride 4mg or placebo, once daily; duration 12-weeks		
Fleshner et. al.[49]	Prostate cancer	dutasteride 0.5mg or matching placebo, once daily; duration 3 years	Pill count	Mean 97% in both groups
Gallwitz et. al.[50]	Type 2 diabetes	linagliptin 5mg tablet and one placebo capsule once daily or one glimepiride(1-4mg titrated dose) capsule and once placebo tablet, once daily; duration 104 weeks	Pill count number of tablets/capsules taken, as a percentage of the number that should have been taken. Non-adherence (<80% or >120%) was treated as a protocol violation	At least 93% of patients were adherent