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Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review

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Short title: medication adherence in recent trials

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Abstract (238 words)

Background: International recommendations such as the CONSORT and International Conference on Harmonisation statements recognize patient adherence to prescribed treatment as an important aspect of a treatment's evaluation, but this issue is little assessed.

Objectives: To evaluate how medication adherence was assessed and reported in recently published randomized controlled trials (RCTs).

Material and Methods: All publications of RCTs assessing pharmacological treatments in 6 major chronic diseases published in high-impact-factor journals in 2003 and 2004 were selected from the Medline database. Two investigators analysed how medication adherence was assessed and reported.

Results: A total of 192 publications were analyzed: 71 in HIV infection, 48 diabetes mellitus, 24 rheumatoid arthritis, 23 asthma, 15 hypertension, 7 osteoporosis, and 4 about 2 of these diseases. The assessment of medication adherence was documented in 69 (35.9%) publications, by counting pill intake in half of these. Results of adherence were reported in 64 (33.3%) publications. Adherence was reported as a quantitative measure: proportion of the treatment prescribed in 27 articles and as a qualitative measure (adherent patient, yes/no) in 41 (in 4 reports both techniques were used). When reported, the median intake of prescribed medication was 93%, and the median proportion of "nonadherent" patients was 6.2%.

Conclusion: There is important variability in the assessment and reporting of medication adherence in published RCTs of pharmacological treatments of selected chronic diseases, for a given disease and across diseases. Standardization is advisable to allow for comparisons among studies.

Introduction

Medication adherence, which can be defined as taking medication as prescribed or as “the extent to which a person’s behavior coincides with medical or health advice”⁽¹⁾, is an essential component of a successful health outcome^(2, 3). Both clinical experience and the literature describe medication adherence as frequently inadequate: at least 50% of patients unintentionally omit doses⁽³⁻⁷⁾. Adherence is particularly important in chronic diseases: the average adherence with long-term medical regimens is estimated at 50% to 65%⁽⁸⁾.

Measurement of medication adherence has been recognized as an important factor in medical care and treatment outcome^(1, 9). Moreover, the CONSORT statement for the reporting of randomized controlled trials recommends showing the flow of participants through each stage of a randomized controlled trial and including, in the item for follow-up, “the number of participants who completed treatment as allocated and the number who did not complete treatment as allocated, by study group”⁽¹⁰⁾. Completing treatment includes the notion of taking the medication (i.e., adherence). Furthermore, the International Conference on Harmonisation (ICH) guidelines also include recommendations to report adherence: “the measures taken to ensure and document treatment adherence should be described, e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring”⁽¹¹⁾. Thus adherence is an important issue in clinical practice in chronic diseases and has been recognized by major instances as an important issue for randomized controlled trials.

However, data on whether these recommendations are applied or the methodological issues of medication adherence for randomized controlled trials are

lacking^(12, 13) and even articles describing adherence consider it only in a particular context (e.g., definitions of adherence when electronic event-monitoring devices are used)⁽¹³⁾.

The complexity of the problem regarding adherence has prevented the development of a gold standard method of measurement and the lack of a valid measure of nonadherence is itself a major barrier to adherence research. The first methodological difficulty in the issue of medication adherence is assessment. Several methods to assess adherence have been proposed; some are based on patient recall (patient diary, patient questionnaire⁹), and others on more objective methods (pill count, blood drug concentrations, or devices such as electronic medication-event monitoring^{3, 14}). To our knowledge, no systematic review of the techniques used to measure adherence in clinical trials exists. Another difficulty concerns the reporting of adherence. Adherence can be reported either as a quantitative measure (i.e., as a proportion of prescribed treatment) or as a qualitative measure, i.e., adherent versus nonadherent patients). Finally, another aspect of interest concerns the possible effect of nonadherence on the interpretation of trial results. For example, for a given sample size, nonadherence, like follow-up loss, lowers the study power⁽¹⁵⁾.

The objectives of this study were to 1) evaluate recent publications of randomized controlled trials of treatment of 6 chronic diseases (HIV infection, asthma, rheumatoid arthritis, diabetes mellitus, hypertension, and osteoporosis) to determine documentation of frequency of medication adherence assessment and 2) determine which methods are used to assess and report adherence. The goal is not to be exhaustive but, rather, to report a “pilot study” of methodological issues concerning adherence.

Material and methods

A systematic review of recent randomized controlled trials was performed. Publications of 6 major chronic diseases were included: HIV infection, asthma, rheumatoid arthritis, diabetes mellitus, hypertension, and osteoporosis. These diseases offer a range of different situations and potentially different methodological difficulties for assessing adherence, since some are asymptomatic and some require polymedication.

1. Search strategy

We selected publications of all randomized controlled clinical trials assessing self-administered pharmacological interventions in patients with one of the 6 chronic diseases and published over 2 years, between January 1, 2003, and December 31, 2004, from journals that publish randomized controlled trials: 6 of the highest-impact-factor general and internal medicine journals and 4 journals with the highest impact factor for each concerned specialty (Journal Citation Reports 2003; list of journals is in appendix).

Publications were identified in the Medline database through a search that used the following exploded MeSH terms: “asthma OR antiasthmatic agents,” “diabetes mellitus,” “rheumatoid arthritis,” “HIV infections OR acquired immunodeficiency syndrome,” “hypertension OR antihypertensive agents,” and “osteoporosis,” with a limitation to “Randomized Clinical Trials”, “Humans” and English-language articles.

Publications were included only if the study design was identified as a randomized controlled clinical trial, published as a full-text article and assessed a pharmacological treatment self-administered by adult patients with one of the 6

selected diseases. Results of the article selection process are reported in Figure 1 (date of article selection process: February 17, 2005).

2. Method for evaluation of publications

Publications were evaluated based on the full-text articles. The reviewer was not blinded to the journal name and the authors, as evidence concerning the effect of masking on assessments of trial quality is inconsistent^(16, 17).

A standardised checklist of items was used to collect data from each article. The checklist was developed by the 2 reviewers, LG and FT, in a separate set of articles published in 2002; the interpretation of the different scales was discussed to resolve any differences in scoring beforehand. (The checklist is available from the authors). During the study, one reviewer (LG) evaluated all the articles and the second reviewer (FT) independently examined 30 articles chosen randomly; comparison of the results obtained for these 30 articles allowed us to calculate inter-rater reproducibility.

Abstracted data included year of publication, funding sources (public or private either clearly reported or extrapolated from authors' affiliations), number of centers involved, underlying disease, trial duration, type of treatment assessed (symptom modifying versus disease controlling), number of treatments taken simultaneously by a patient during the trial and planned in the study design (even if only some of these treatments were evaluated), route of administration (oral, topical, subcutaneous, inhalation, other).

The quality of the publications was determined by use of the Jadad scale⁽¹⁸⁾ (score 0 to 5) and the Delphi list^(19, 20) (score 0 to 9). A high score indicates high quality for both scales.

3. Evaluation of adherence

Assessment and reporting of adherence

It was checked whether adherence was described as being assessed in the Materials and methods section of each article. If so, the technique or techniques used to assess adherence were noted, as well as the moment of evaluation and the assessor. When reported, methods used to measure adherence were recorded in detail and classified into methods based on the care provider (e.g., pill count, physical examination for frequent clinical adverse effects), patients (patients' self-report [e.g., written or electronic diary], elicited report [e.g., global or specific questioning], or other methods), use of devices (e.g., pill count by electronic monitoring^{3, 14}), biologic elements (e.g., serum levels, urine levels, measurement of expected biologic effects) or other methods.

How adherence was reported and adherence results were noted if available and if available results were noted in the different treatment arms.

Reporting of trial results

It was checked whether adherence was an outcome measure for the trial, and since nonadherence can lower the power of a study⁽¹⁵⁾, it was checked whether nonadherence was taken into account in the sample size calculations.

Elements associated with reporting of adherence in a publication

As an exploratory analysis, it was checked what elements predicted reporting of adherence. The trial or publication characteristics investigated for association with reporting of adherence (yes/no) were the disease, journal, journal impact factor, type of funding, number of patients, trial duration, number of centers, dates of the trial,

whether it was the first publication from a trial, intention-to-treat analysis and methodologic quality of the publication.

4. Statistical analysis

Comparisons between variables involved Fisher's exact test or the Mann-Whitney nonparametric test, as appropriate. Inter-rater reliability between the 2 reviewers was assessed by use of the intraclass correlation coefficient (ICC) for continuous variables and Kappa statistic for qualitative variables. Nonparametric univariate analysis and multivariate stepwise logistic regression were performed between reporting of adherence (yes/no) and trial and publication characteristics. All data analyses involved use of the Statistical Analysis System (SAS) version 9.1.

Results

1. Selected publications

Of the 637 publications identified, 192 were included in the analysis (Figure 1). The 445 publications excluded were mainly not randomized controlled trials (n=91), not assessing a pharmacological therapeutic intervention (n=131), or not about the selected diseases (n=72).

The characteristics of the publications are given in Table 1. Publications described mainly trials in HIV infection (n= 71, 37%) and diabetes mellitus (n= 48, 25%). Thirty percent of the reports were published in general medical journals. Financial support was totally or partially public in 45.8%, private in 43.7% and not reported in 10.4%.

Patients took a median of 2 medications, with more medications per trial in reports of HIV trials; the route of administration was mainly oral (81.8%). The types of medications were mainly disease controlling (n= 160 trials, 83.3%) or preventive, either of the target disease (n= 7 trials, 3.6%) or of a complication (n= 12 publications, 6.3%). The median duration of intake of the medications (without a run-in period) was 48 weeks and the median number of patients participating in the trials was 185; these characteristics varied greatly across diseases.

Items of the CONSORT diagram ⁽¹¹⁾ (flow of participants through each stage of the trial) were reported in a flow chart or in the text in 68.3% of the publications.

The median quality of the articles was high: 3 on the 5-point Jadad scale and 7 on the 9-point Delphi list.

Inter-rater reliability was good: for mention of adherence (kappa=0.93 [95% confidence interval (CI)=0.81-1.00]), assessment of adherence (kappa=0.93 [95% CI=0.81-1.00]), reporting of adherence (kappa=0.85 [95% CI=0.75-1.00]), the Jadad

scale (ICC=0.84 [95% CI=0.69-0.92]) and the Delphi list (ICC=0.85 [95% CI=0.72-0.93]).

2. Assessment of adherence

Adherence was described as assessed in 69 (35.9%) publications. However, data on methods of assessment was missing in 8 of these (11.6%).

Table 2 shows the techniques described to assess adherence according to the disease. The techniques most frequently described were pill count (n= 34, 49.3% of the 69 publications) and patient diary (n= 15, 21.7%), but patient diary was the only technique in only 8 of the publications (11.6%).

Two or more techniques were described in 18 publications (26.1%) and this was not more frequent in one disease than in another (p=0.85). Separate results for the different techniques were given in only 2 of these publications (11.1%); in fact, in all the other cases determining which of the techniques had produced the given results was impossible. In most cases (n= 60 publications, 86.7% of 69), all patients were evaluated for adherence. Assessments of adherence were described as performed at every visit in 44 (63.8%) cases, at specified visits in 11 (15.9%), and this was not available in 14 (20.3%). When several drugs were taken, it was not always clear which drugs were evaluated for adherence (data unclear in 12 publications, 37.5% of 32 publications with several drugs and assessment).

3. Reporting of adherence

Adherence was reported in 64 publications (33.3%). However in 21 articles (10.9%) adherence was reported to be assessed but no results were given, and in 26 other articles (13.5%) no elements for how adherence was assessed were given, but

adherence results were reported (this explains discrepancies between assessment and reporting of adherence as seen Table 1).

Adherence was reported either as a quantitative measure, i.e., as a proportion of prescribed treatment (e.g., intake is 67% of the prescribed dosage): in 27 publications (14.1% of 192), or as a qualitative measure (i.e., adherent versus nonadherent patients e.g., 17 patients were nonadherent): in 41 publications (21.4% of 192). In 4 publications (2.1%), adherence was reported both as a qualitative and a quantitative measure (often as excluded patients in the CONSORT flow-chart and as a proportion of medication taken).

Reports defining adherence qualitatively (n= 41; 21.4%) described a cutoff point (e.g., a patient was nonadherent if intake was less than 80% of total medication). In 10 reports (24.4%) several cutoffs were described. In 8 publications, cutoff was 80% of medication, and in 6 cutoff was 80% of treatment for 80% of the time. In 7 publications, a definition of adherence was “patients totally adherent,” and other cutoffs used (19 times) varied among studies, ranging from “at least one intake (>0%)” to “patients missing just one dose.” In 3 cases (7.3%), the cutoff used was unclear. In 23 publications (12.0%), “number of patients excluded for nonadherence” was reported, mainly presented in the CONSORT flow chart (18 publications).

When adherence was reported as a quantitative measure, we could distinguish between dose-taking and dose-timing adherence. Dose-taking measures (quantitative adherence) assess whether the appropriate number of doses were taken and dose-timing measures assess whether the doses were taken within the appropriate time interval during the day (e.g., within 25% of the dosing interval). Dose-timing adherence was described in only 4 publications (the same 4

publications describing electronic monitoring assessment). In only these reports were extra doses (not just missed doses) also taken into account for the definition of adherence.

4. Adherence results and trial results

When adherence was reported as a qualitative measure (41 publications), the median percentage of “nonadherent” patients was 6.2% (range 0-63.3%) and was similar across the treatment arms, when reported. In the 27 publications in which adherence was reported as a quantitative measure, the median reported adherence was 93% (i.e., intake of 93% of the medication prescribed over the trial duration, range 63.5-100%). Adherence was reported separately in the different trial arms in 41 publications (64.1%), and 22 (31.9%) specified whether adherence was similar in the treatment arms.

Adherence was described as an outcome measure in 5 cases (2.6%). Five publications (2.6%) documented a run-in period where adherence was evaluated. Calculation of the sample size was reported in 125 (65.1%); however, the sample size took into account predicted nonadherence in only 2 (1.6% of 125).

The probability value for the primary outcome measure was available in 164 reports (82.8%); in 130 (79.3%) the p value was significant (<0.05) and did not differ according to whether adherence was reported or not ($p=0.68$).

5. Elements associated with reporting of adherence

The exploratory multivariate analysis revealed that the only elements associated with reporting of adherence were the methodologic quality of the publication (Jadad

score: $p=0.0007$; for an increase of one point of Jadad score, $OR=1.80$ [95% $CI=1.28-2.52$] and the disease ($p=0.04$): adherence was more often reported in reports of osteoporosis (71.4%), asthma (41.7%) and HIV infection (40.9%) than in reports of other diseases.

Discussion

This study assessed the methodological variability in the field of medication adherence in reports of randomized controlled trials of self-administered pharmacological interventions for 6 chronic diseases published over 2 years in high-impact general medical and specialty journals. To our knowledge, this is the first description of methods used to assess adherence in a diverse sample of trials in different chronic conditions. It provides an unprecedented look into the assessment and reporting of adherence in randomized controlled trials, revealing some clear and relevant disparities in the definitions of adherence and methods used to report the results.

The CONSORT statement and the ICH guidelines both encourage the reporting of adherence ^(10, 11). Despite consistent recommendations for reporting adherence in clinical trials, our literature review showed results for adherence were reported in only 33% of the publications we assessed, and even less often were assessment methods and results given (25%). Furthermore, in the 33% publications, adherence was reported as extremely high. Of course, these results give rise to speculation regarding the results in the other studies that did not report adherence. Thus, a discrepancy exists between what is recommended and what we observed, even in recent reports published in high-impact-factor journals with a high methodological quality (both according to the Jadad scale and the Delphi list).

There are some possible explanations for this discrepancy. A simple explanation could arise from size constraints for published articles, which force the authors, sometimes even at the reviewers' instigation, to omit some elements from their

publications ⁽²¹⁾. In favour of this explanation, we note that 22 publications (11.5%) included some information on either assessment or definition of adherence but no results on adherence. Thus, a limitation to our study is that we assessed only publications of randomized controlled trials, not the trials themselves.

Another important element that could explain the underreporting of adherence is related to the methodological difficulties of how to assess and synthesize and report the results of adherence. As indicated by our literature review, to date no consensus exists on these aspects. In the evaluated publications, adherence was assessed mainly by pill count, but many other techniques were used. Methods of assessment were detailed in only 31.8% of publications, despite literature indicating that results of adherence depend greatly on the technique of assessment ⁽²²⁻²⁶⁾.

We also noted great heterogeneity in the definitions of adherence, whether proportion of the medication prescribed or adherent patient (yes/no), and in the latter case, a large range of cutoffs was described. When adherence was defined as a quantitative measure, it was almost always a proportion of the prescribed treatment taken. For qualitative cutoffs, the most frequent cutoff was “patient excluded for nonadherence,” which is not a reproducible definition of nonadherence and indeed can refer to nonadherence to the protocol as well as to the treatment. When a numerical cutoff was given for nonadherence, results varied widely among diseases studied and for a given disease, which makes comparisons between studies (and interpretations of differences in effect size) difficult.

Results of clinical trials can be influenced by patient adherence ^(27, 28). Nonadherence leads to loss of power for a given sample size, which can lead to

negative results for trials ⁽¹⁵⁾, even if a treatment is efficacious, and this element was rarely taken into account in the publications we assessed. Treatment failures that are usually assumed to be medication failures may be a result of nonadherence rather than lack of efficacy. Thus, adherence should be reported and considered when interpreting the results of a trial.

The limitations of our study include the selection of high-impact-factor journals. We chose these journals because a high impact factor is a good predictor of higher methodological quality of journal articles ⁽²⁹⁾ and because our goal was not to be exhaustive but, rather, to raise awareness of methodological issues concerning assessment and reporting of adherence. Furthermore, since we found reporting of adherence to be associated with methodological quality, we doubt that adherence could be reported more in low-impact-factor journals. Another limitation is that we chose only 6 diseases; however, these diseases represent a range of difficulties with regard to adherence. This comparison allowed us to point out that adherence was significantly more often mentioned in reports of osteoporosis, asthma and HIV infection, which may reflect the habits and methods of disease trialists.

To our knowledge, this is the first study comparing the methodology used to measure adherence in different diseases. Clearly, there is room for standardization across specialties. Finally, we have studied only chronic diseases; but chronic diseases are the most relevant for studying adherence, since chronic conditions carry with them the issue of medication adherence ⁽⁸⁾.

In conclusion, this study allowed us to point out the real difficulties in the assessment, definition and reporting of medication adherence in randomized

controlled trials. Reporting adherence is widely recommended^(10, 11); furthermore, to allow comparisons of trials by systematic review and meta-analysis, our study highlights the need for further research in this domain for standardization of the assessment, definition and reporting of medication adherence in trials. In particular, emphasis should to be given to determining which measure of adherence is preferable.

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References

1. Haynes RB, Taylor DW, Sackett DL, eds. Compliance in healthcare. Baltimore: The John Hopkins University Press; 1979.
2. Cramer J, Rosenheck R, Kirk G, et al. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. Value Health. 2003;6: 566-73.
3. Haynes RB, Sackett DL, Gibson ES, et al. Improvement of medication compliance in uncontrolled hypertension. Lancet 1976;1:1265-8.
4. Blackwell B. From compliance to alliance: a quarter century of research. Neth J Med. 1996;48:140-9.
5. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.
6. Christensen DB. Drug-taking compliance: a review and synthesis. Health Serv Res. 1978; 198:171-187.
7. Cramer JA. Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. Am J Managed Care. 1998;4:1563-8.
8. Haynes RB, Dantes R. Patient compliance and the conduct and interpretation of clinical trials. Controlled Clinical Trials 1987, 8:12-9.
9. Cramer JA, Spilker B, eds. Patient compliance in medical practice and clinical trials. New York: Raven Press; 1991.
10. Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285:1987-91.

11. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Structure and content of clinical study reports, E3. <http://www.ich.org>
12. Nichol MB, Venturini F, Sung JC. A critical evaluation of the methodology of the literature on medication compliance. *Ann Pharmacother.* 1999;33:531-40.
13. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001;23:1296-310.
14. Olivieri NF, Matsui D, Hermann C, et al. Compliance assessed by the Medication Event Monitoring System. *Arch Dis Child.* 1991;66:1399-402.
15. Lang JM, Buring JE, Rosner B, et al. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med* 1991;10:1585-93.
16. van Rooyen S, Godlee F, Evans S, et al. Effect of blinding and unmasking on the quality of peer review: a randomized trial. *Jama.* 1998;280:234-7.
17. Justice AC, Berlin JA, Fletcher SW, et al. Do readers and peer reviewers agree on manuscript quality? *JAMA.* 1994;272:117-9.
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1-12.
19. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol.* 1998;51:1235-41.
20. Verhagen AP, de Vet HC, Vermeer F, et al. The influence of methodologic quality on the conclusion of a landmark meta-analysis on thrombolytic therapy. *Int J Technol Assess Health Care.* 2002;18:11-23.

21. Hill CL LM, Felson DT. Discrepancy between published report and actual conduct of randomized clinical trials. *J Clin Epidemiol.* 2002(55):783-6.
22. Maenpaa H, Manninen V, Heinonen OP. Comparison of the digoxin marker with capsule counting and compliance questionnaire methods for measuring compliance to medication in a clinical trial. *Eur Heart J.* 1987;8:39-43.
23. Melkinow J, Kiefe C. Patient compliance and medical research: issues in methodology. *J Gen Intern Med* 1994; 9:96-105.
24. Rudd P, Byyny RL, Zachary V, et al. The natural history of medication compliance in a drug trial: limitations of pill counts. *Clin Pharmacol Ther* 1989;46:169-76.
25. Caron HS. Compliance: the case for objective measurement. *J Hypertens* 1985;3(suppl 1):11-7.
26. Mushlin AI, Appel FA. Diagnosing potential non-compliance: physician's ability in a behavioral dimension of medical care. *Arch Intern Med* 1977;137:318.
27. Lindsey JC, McGrath NM. Interpreting treatment differences when patients drop out of a clinical trial. *AIDS Patient Care STDS.* 1998;12:275-85.
28. Hogan JW, Laird NM. Intention-to-treat analyses for incomplete repeated measures data. *Biometrics* 1996; 52:1002-17.
29. Lee KP, Schotland M, Bacchetti P, et al. Association of journal quality indicators with methodological quality of clinical research articles. *JAMA* 2002;287:2805-8.

Figure 1: Screening process

