Systematic Literature Review and Meta-analysis of Medication Adherence With Once-weekly Versus Once-daily Therapy

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ABSTRACT

Purpose: To compare medication adherence rates for once-weekly (QW) versus once-daily (QD) dosing regimens in patients with chronic disease.

Methods: A systematic literature review was conducted to identify articles published in English-language journals examining the rate of adherence to medications in patients with chronic disease. Relevant studies were identified from January 2002 through August 2013 using PubMed, EMBASE, and the Cochrane Library databases. Twenty-two published observational studies reporting adherence were identified by 2 independent reviewers, and 7 articles reported relevant measures for analysis. All studies were conducted in patients with osteoporosis. Meta-analyses estimated (1) mean difference (MD) in adherence (defined using the mean medication possession ratio [MPR]) between QW and QD dosing groups and (2) odds ratio (OR) for adherence (defined using an MPR cutoff of $\geq$80%) for QW versus QD dosing. Heterogeneity was assessed using Cochran's Q and I^2 values, and meta-analyses used both fixed- and random-effects models.

Findings: The random-effects meta-analysis revealed a significantly greater MPR with QW compared with QD dosing (pooled MD = 12.29%; 95% CI, 10.76%–13.82%; n = 9 [data reported in 7 publications]). Because of the high level of heterogeneity (I^2 = 83.4%), the fixed-effects model results were not appropriate to report for the pooled MD. When examining the OR for adherence, both fixed- and random-effects models provided similar results due to the low level of heterogeneity (I^2 = 7.9%; n = 5 [data reported in 3 publications]). Using either model, the pooled odds of being adherent (MPR $\geq$80%) in the QW dosing group was approximately 1.9 times the odds in the QD dosing group (random-effects OR = 1.90; 95% CI, 1.81–2.00; fixed-effects OR = 1.92; 95% CI, 1.84–1.99).

Implications: In our meta-analysis, QW dosing was associated with better adherence levels and greater odds of being adherent compared with QD dosing in patients with osteoporosis. (*Clin Ther*. 2015;37:1813–1821)

Key words: adherence, daily dosing, dosing regimen, medication possession ratio, osteoporosis, weekly dosing.

INTRODUCTION

Chronic diseases are the leading cause of morbidity and mortality worldwide, accounting for approximately 60% of all deaths and 43% of the global burden of disease. These numbers are only expected to increase, and by 2020, it is estimated that chronic diseases will be responsible for 73% of all deaths.[1]

Although chronic conditions can often be managed by pharmacologic therapy, if medications are not taken as prescribed, the clinical benefit can be substantially reduced. The World Health Organization estimates that the rate of nonadherence to long-term therapy in chronic diseases is approximately 50%, with rates even higher in developing countries.[2] Furthermore, in the United States, poor adherence is implicated in 33% to 69% of all medication-related hospitalizations, and results in a cost of about $100 billion per year.[3] Because chronic conditions constitute a long course of treatment, an additional complicating issue is the fact that adherence

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tends to decrease over time, most significantly after the first 6 months of therapy.[4]

Previous research has suggested that medication adherence is influenced by many factors, including dosing frequency.[3] One approach that has been suggested to improve medication adherence in these patients is to reduce the dosing frequency of medication. Several published studies have evaluated the effect of dosing frequency on medication adherence, with most indicating that reduced dosing improves patient adherence and patients prefer a less frequent dosing schedule [5–8] however, no studies to our knowledge have conducted a meta-analysis using published observational studies to primarily examine medication adherence for once-daily (QD) and once-weekly (QW) dosing regimens.

METHODS

Literature Search

A systematic literature review was conducted to identify articles evaluating the rate of adherence to medications in patients with chronic disease. Relevant studies were identified using PubMed, EMBASE, and the Cochrane Library databases. The search strategy included both free text and medical subject heading terms related to medication adherence or compliance and weekly dosing (**Supplemental Appendix**). A manual search of the reference lists from relevant review articles identified any additional publications that might not have been included in the search results. We limited our search to articles published in English-language journals from January 2002 through August 2013.

Selection Criteria

All articles from the 3 databases were screened by 2 independent reviewers (K.I., K.J.). Studies were included if they met the following criteria: The study must (1) be conducted in adults with noninfectious chronic disease, (2) a primary publication, (3) quantify adherence or compliance and contain an adequate description of the methods used, and (4) compare QD and QW dosing of pharmacologic treatments.

Studies were excluded from the analysis if they assessed adherence to contraception or vitamin supplements, were studies of patients with cancer, or were animal studies; if the full-text article was not available and the abstract did not provide sufficient information on the methods; or if the study design was a randomized clinical trial (RCT). Because of the stringent follow-up implemented in RCTs, they often do not provide a real-world assessment of adherence. Thus, RCTs were not considered relevant for this analysis. Conference abstracts were included as long as they contained sufficient information on the study methods.

Data Abstraction and Quality Assessment

The 2 independent reviewers abstracted the data from selected articles using a standardized data abstraction form. Extracted information included study design, length of study or observation period, country or region, data source(s), study objective, inclusion and exclusion criteria, sample size, patient age, patient sex, chronic disease type, dosing regimen studied, specific therapeutic agents examined, concurrent medications, baseline comorbidities, baseline laboratory measures, baseline body mass index, baseline weight or other weight measure (eg, waist circumference), bone mineral density, study outcomes, measure used to assess medication adherence, how treatment adherence measure is defined, length of time within study used to assess adherence measure, reported adherence results, follow-up laboratory values, follow-up body mass index, follow-up weight or other weight measure, adverse events, study conclusions, and study limitations. Data were cross-checked by the reviewers, and any discrepancies were discussed and resolved through a consensus. All abstracted articles were independently assessed for quality by each reviewer using the Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies. This validated instrument is recommended by the Cochrane Collaboration in the *Cochrane Handbook for Systematic Reviews of Interventions*.[9–11]

Adherence Assessment

According to the International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group, medication compliance and medication adherence are synonyms referring to "the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking."[12] One of the most common ways to quantify adherence is through the use of the medication possession ratio (MPR). This calculation is computed by summing the number of days a patient is supplied with medication