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 ≥80%) for QW versus QD dosing. Heterogeneity was assessed using Cochran’s Q and I² 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 (I² = 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 (I² = 7.9%; n = 5 [data reported in 3 publications]). Using either model, the pooled odds of being adherent (MPR ≥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) © 2015 Elsevier HS Journals, Inc. All rights reserved.

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
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.5 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 schedule5–8 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
for all but the last refill and then dividing by the number of days between the first and last refills. This equation can be modified in the case of combination therapy or when the researcher prefers to use a fixed time frame as the denominator. The MPR can also be assessed as a dichotomous variable, where a cut point is determined to identify patients considered adherent versus nonadherent. In studies of chronic, noninfectious disease, patients with an MPR ≥80% during the study period are generally labeled as being adherent.

**Statistical Analysis**

The measures calculated in this analysis were (1) mean difference (MD) in adherence between the QW and QD dosing groups and (2) odds ratio (OR) of adherence for QW versus QD dosing. The MD was calculated by determining the MPR for the QD and QW cohorts in each study and then calculating the difference of the means between the 2 groups. To calculate the OR, adherence was defined as a dichotomous variable using an MPR cut-off of ≥80%. Heterogeneity was evaluated using Cochran’s Q and I² values. The Mantel-Haenszel method (fixed-effects model) was performed in the case of low to moderate heterogeneity, and the DerSimonian-Laird method (weighted inverse variance random-effects model) was performed to account for high heterogeneity among studies. Because of the limited number of studies, no subgroup analyses or metaregressions were performed.

**RESULTS**

**Systematic Literature Review**

The electronic search returned 3617 articles, and a manual search of the references uncovered an additional 7 publications. Of these articles, 1685 duplicates were removed, leaving 1939 records to be screened. On screening these abstracts, the reviewers excluded 1638 articles because they did not meet the inclusion and exclusion criteria. The 301 articles that remained had their full texts screened for eligibility. Of these, 279 were excluded because they met the following criteria: did not measure or quantify adherence or compliance (66 articles), were a review or meta-analysis (50 articles), had no QW vs QD comparison (40 articles), were a study or publication type other than primary (39 articles), used a pediatric population (22 articles), patient-reported outcome study (16 articles), did not compare pharmacologic treatments (15 articles), studied a disease that was nonchronic in nature (14 articles), examined the use of dietary supplements (12 articles), had no full text available in English or no abstract or full-text available (4 articles), or had an insufficient description of methods (1 article).

Twenty-two publications met all the inclusion criteria and underwent data extraction. Of these articles, 14 were excluded for the following reasons: defined MPR differently (ie, use of a variable instead of fixed denominator) or did not measure MPR (6 articles), patients were allowed to change dose during the assessment period (4 articles), insufficient data points or methods (3 articles), or same patient sample as another study (1 article). Although the original intent was to examine all chronic diseases, only 1 of the remaining articles found in our search was not conducted in patients with osteoporosis. To maintain a homogenous sample for the meta-analysis, this additional publication was excluded.

After excluding a total of 15 articles, 7 publications remained and were included in the meta-analysis. All 7 articles reported mean MPR, whereas only 3 reported an MPR ≥80%. Figure 1 shows the different phases of review. After thorough review of those articles, 9 individual retrospective database studies were identified from the 7 publications and were included in the meta-analysis for MD in MPR. Among them, only 5 studies from 3 publications reported the proportion of patients with an MPR ≥80%. A total of 65,679 patients were included in the adherence analyses across multiple countries (United States, United Kingdom, Belgium, France, and Israel), with follow-up ranging from 12 to 13 months. Study populations were comparable, all including women who were initiating treatment with bisphosphonates. Patients were not allowed to change dosing regimens during the follow-up period. Characteristics of the 9 studies are summarized in the Table.13–19

**Meta-analysis: Mean Difference in MPR**

Significant heterogeneity was found with a Q statistic of 48.2 (P < 0.0001) and I² of 83.4%, rejecting the hypothesis that all studies share the same MD. Therefore, a random-effects model was used to account for the heterogeneity among studies. 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 studies) (Figure 2).

On closer review, 1 analysis in the article by Brankin et al.13 using the Doctors Independent Network Database (DIN-LINK) reported extremely narrow CIs given the sample size. Without having access to patient-level data, these results could not be verified. To ensure the accuracy of our results, we performed a sensitivity analysis removing the DIN-LINK analysis for the outcome of MD. A high degree of heterogeneity remained (Q = 41.55; P < 0.0001; and I² = 83.2%); therefore, a random-effects model was used for the sensitivity analysis. The random-effects meta-analysis of the remaining 8 studies still found a significantly greater MPR with QW compared with QD dosing (pooled MD =11.69%; 95% CI, 9.35%–14.03%).

**Meta-analysis: OR for Adherence**

Among the 5 studies included in the meta-analysis for the pooled OR, a low level of heterogeneity was observed (Q = 4.34; P = 0.36; I² = 7.9%). Using either model, the pooled odds of being adherent (MPR ≥ 80%) in the QW dosing group was approximately 1.9 times the odds in the QD dosing group (random-effects OR = 1.90;
## Table. Studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Data Source (Country)</th>
<th>Database Used</th>
<th>Follow-up Period, mo</th>
<th>Sample Size</th>
<th>Mean (SD) Age, y</th>
<th>Treatments Evaluated for Adherence Analysis</th>
<th>Study Quality</th>
<th>Mean MPR</th>
<th>MPR ≥ 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brankin, 2006</td>
<td>UK</td>
<td>GPRD, IMS Disease Analyzer (MEDIPLUS) and the DIN-LINK</td>
<td>12</td>
<td>GPRD: 7567, MEDIPLUS: 5962, DIN-LINK: 1801</td>
<td>GPRD: 71.7 (10.1), MEDIPLUS: 72.9 (10.3), DIN-LINK: 70.5 (10.1)</td>
<td>Alendronate, risedronate</td>
<td>Moderate</td>
<td>GPRD: QD: 63.5%, QW: 76.2% (P &lt; 0.0001)</td>
<td>GPRD: QD: 51.2%, QW: 65.3% (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Cramer et al, 2005</td>
<td>United States</td>
<td>Health care claims database</td>
<td>13</td>
<td>2741</td>
<td>NR</td>
<td>Alendronate, risedronate</td>
<td>Strong</td>
<td>QD: 57.6% (56.0–59.2), QW: 69.2% (66.7–71.3) (P &lt; 0.0001)</td>
<td>QD: 40.4%, QW: 55.3% (P ≤ 0.0001)</td>
</tr>
<tr>
<td>Cramer et al, 2006</td>
<td>France</td>
<td>Thales (France)</td>
<td>12</td>
<td>France: 5332, France: 69.7</td>
<td>Alendronate, risedronate</td>
<td>Moderate</td>
<td>France: QD: 53%, QW: 59% (P &lt; 0.001)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Downey et al, 2006</td>
<td>United States</td>
<td>National managed care administrative claims database</td>
<td>12</td>
<td>Total: 10,566, Adherence analysis: 8365</td>
<td>64.4 (10.4)</td>
<td>Alendronate, risedronate</td>
<td>Strong</td>
<td>QD: 53.8%, QW: 62.5% (P &lt; 0.05)</td>
<td>NR</td>
</tr>
<tr>
<td>Kertes et al, 2008</td>
<td>Israel</td>
<td>Maccabi HealthCare Services database</td>
<td>12</td>
<td>Total: 4448, Excluding switchers: 3937</td>
<td>NR</td>
<td>Alendronate, risedronate</td>
<td>Strong</td>
<td>QD: 52% QW: 70% Switched to QW: 79% Mixed: 83% (P &lt; 0.001)</td>
<td>NR</td>
</tr>
<tr>
<td>Rabenda et al, 2008</td>
<td>Belgium</td>
<td>Belgian national social security database</td>
<td>12</td>
<td>Total: 142,302, Adherence analysis: 29,157</td>
<td>NR</td>
<td>Alendronate</td>
<td>Moderate</td>
<td>QD: 58.6% QW: 70.5% (P &lt; 0.001)</td>
<td>QD: 40.4% QW: 57%</td>
</tr>
<tr>
<td>Rabenda et al, 2008</td>
<td>Belgium</td>
<td>Belgian national social security database</td>
<td>12</td>
<td>Total: 23,146, Adherence analysis: 306</td>
<td>NR</td>
<td>Alendronate</td>
<td>Moderate</td>
<td>QD: 65.9% QW: 67.7% (P = 0.65)</td>
<td>NR</td>
</tr>
</tbody>
</table>

DIN-LINK = Doctors Independent Network Database; GPRD = General Practice Research Database; NR = not reported; QD = once daily; QW = once weekly.
DISCUSSION

In the present study, results from 9 observational studies were synthesized to evaluate the effect of dosing frequency on medication adherence. Most studies were conducted in patients with osteoporosis. The only study that was not conducted in patients with osteoporosis was excluded to maintain a homogenous study sample. Osteoporosis is a progressive skeletal disease that causes low bone density and microarchitectural deterioration, leading to frail bones and an increased fracture risk.\textsuperscript{15,20–22} Osteoporosis affects >200 million women worldwide and is especially common among postmenopausal women aged ≥50 years. More specifically, approximately 10% of women aged 60 years, 20% of women aged 70 years, 40% of women aged 80 years, and 66% of women aged 90 years face an osteoporosis diagnosis. Approved pharmacologic treatment options for osteoporosis include bisphosphonates, estrogens and/or hormone therapy, tissue-selective estrogen complex, parathyroid hormone 1–34, and Receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor.\textsuperscript{23}

Although pharmacologic therapies for osteoporosis are widely available, 8.9 million patients still experience a fracture each year as a result of their condition.\textsuperscript{24} A portion of this fracture burden has been attributed to poor adherence to osteoporosis therapy.\textsuperscript{24} Previous studies have estimated that the percentage of patients continuing with osteoporosis therapy at 1 year could be as low as 25%, and the amount of time patients actually have their medication on hand could be <60%.\textsuperscript{22,25} Our study found that QW dosing was associated with higher MPR values and greater odds of being adherent compared with QD dosing for patients with osteoporosis. These results are consistent with findings from published meta-analyses suggesting that decreased dosing frequency improves adherence of non–osteoporosis-specific therapies.\textsuperscript{26–28}

Medication adherence is a complex issue, but any factor that could simplify medication-taking behavior has the potential of improving medication adherence. QD dosing has been observed to improve adherence versus more frequent dosing regimens in many chronic diseases, including but not limited to chronic obstructive pulmonary disease, chronic renal impairment, and cardiovascular diseases.\textsuperscript{29,30} The availability of QW dosing is still limited to few disease areas, such as type 2 diabetes and osteoporosis. Therefore, the impact of further reduced dosing frequency on medication adherence is difficult to evaluate outside these disease areas. This study found improvement in adherence for QW versus QD dosing among patients with osteoporosis. Despite the observed trend toward better medication adherence for medications with lower dosing frequency, we cannot generalize these results to cases where further reduction in dosing frequency may be feasible.

This study has certain limitations. First, measures of adherence are based on MPR, which only indicates that a prescription was filled. It is unknown whether the medication was actually taken by the patient or taken as directed. Second, as with any literature review and meta-analysis, there is the potential for publication bias. Third, all included articles were in the English language and limited to those published between 2002 and 2013. Therefore, these studies might not represent the larger pool of all adherence studies available in the literature. Fourth, because of the small number of studies meeting our inclusion criteria for the meta-analysis, we could not adjust for potential confounding factors or investigate any interactions. Among the studies included in the meta-analysis, 3 did not report subgroup analyses or assessments for potential confounding factors.\textsuperscript{13,15,18} Of those that did, age was cited as being potentially associated with medication adherence, but the results were mixed. Cramer and colleagues\textsuperscript{14} found that patients aged ≤65 years reported higher MPR values compared with patients aged >65 years, whereas Kertes et al\textsuperscript{17} reported that older age was associated with higher MPR. Rabenda and colleagues\textsuperscript{19} reported patients aged 70 to 79 years had the highest MPR compared with other age groups (<70 and >79 years), whereas Downey et al\textsuperscript{16} found that there was no difference in MPR for patients aged ≥65 years compared with the whole cohort. In addition to age, Kertes et al\textsuperscript{17} also reported that patients who are able to switch between QD and QW dosing regimens, as well as those with a higher level of supplemental insurance, had significantly higher MPR in the multivariate analysis. Another limitation of our study is that the review is focused on QD and QW therapy only and is not generalizable to other osteoporosis dosing regimens. Fifth, because we examined observational studies, significant heterogeneity
Figure 2. Forest plot of medication possession ratio (MPR) mean difference (MD) and 95% CIs. DIN-LINK = Doctors Independent Network Database; GPRD = General Practice Research Database.

Figure 3. Forest plot of the odds ratios (ORs) for adherence and 95% CIs. DIN-LINK = Doctors Independent Network Database; GPRD = General Practice Research Database.
was present across studies for the end point of MD in MPR. Random-effects modeling was used to take this heterogeneity into account, but caution should be used when interpreting the results.

CONCLUSION
In summary, a QW dosing regimen was associated with improved medication adherence compared with the QD dosing regimen in patients with osteoporosis. It is important for physicians to consider the impact of dosing regimens when making treatment decisions, especially in patient subgroups that experience lower levels of adherence.

ACKNOWLEDGMENTS
K.I., K.T., and K.J. were involved in the concept and design of the study. K.I. and K.J. collected and assembled the data, and X.C. and P.M. performed the data analysis. All authors were involved in interpretation of the results. K.I. and S.Y. wrote the initial draft of the article, and all authors were involved in the critical revisions, discussions, and approval of the article.

CONFLICT OF INTEREST
All authors declare that they were full-time employees of Merck & Co, Inc, Kenilworth, New Jersey, at the time of the analysis and may potentially own stock and/or hold stock options in the company. This study was funded by Merck & Co, Inc, Kenilworth, NJ, USA.

SUPPLEMENTARY INFORMATION
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.05.505.

REFERENCES


**SUPPLEMENTAL APPENDIX**

**PubMed**


(2) Weekly[All Fields] OR “once weekly”[All Fields] OR qw[All Fields] OR “once a week”[All Fields] OR “dosing frequency”[All Fields]

(3) “2002/01/01”[PDAT] : “2012/12/31”[PDAT]

(4) “humans”[MeSH Terms]

(5) English[lang]

1 and 2 and 3 and 4 and 5

**EMBASE**

(1) Adherence OR compliance/exp

(2) Weekly OR ‘once weekly’ OR qw OR ‘once a week’ OR ‘dosing frequency’

(3) [humans]/lim

(4) [english]/lim

(5) [embase]/lim

(6) [2002–2012]/py

1 and 2 and 3 and 4 and 5 and 6

**Cochrane Library**

(1) “Medication Adherence” or adherence or “Patient Compliance” or compliance

(2) Weekly or “once weekly” or qw or “once a week” or “dosing frequency”

1 and 2 and limited to publications from 2002–2012