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Relationship Between Daily Dose Frequency and Adherence to Antihypertensive Pharmacotherapy: Evidence from a Meta-Analysis

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ABSTRACT

Background: Rates of patient adherence (compliance) to pharmacotherapy range from <5% to >90%. Negative determinants include multiple daily dosing (MDD), chronic duration, and asymptomatic disease. Reports suggest that once-daily (QD) dosing may improve adherence, but their findings are inconclusive.

Objective: The purpose of this study was to compare the rates of adherence with QD, twice-daily (BID), and MDD antihypertensive drug regimens.

Methods: MEDLINE, Embase, and International Pharmaceutical Abstracts databases were searched to identify comparative trials of patient adherence to antihypertensive medication in solid, oral formulations. Data were combined using a random-effects meta-analytic model.

Results: Eight studies involving a total of 11,485 observations were included (1830 for QD dosing, 4405 for BID dosing, 4147 for dosing >2 times daily [>BID], and 9655 for MDD), in which the primary objective was to assess adherence. The average adherence rate for QD dosing (91.4%, SD = 2.2%) was significantly higher (Z = 4.46, $P < 0.001$) than for MDD (83.2%, SD = 3.5%). This rate was also significantly higher (Z = 2.22, $P = 0.026$) than for BID dosing (92.7% [SD = 2.3%] vs 87.1% [SD = 2.9%]). The difference in adherence rates between BID dosing (90.8%, SD = 4.7%) and >BID dosing (86.3%, SD = 6.7%) was not significant (Z = 1.82, $P = 0.069$).

[*]At the time this research was performed, Michael Iskedjian was a student of the Graduate Department of Pharmaceutical Sciences at the University of Toronto.

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Conclusions: The results of this meta-analysis demonstrate that with antihypertensive medications, QD dosing regimens are associated with higher rates of adherence than either BID or MDD regimens.

Key words: adherence, patient compliance, dosing frequency, daily dose, hypertension, antihypertensive therapy, multiple daily dosing. (*Clin Ther.* 2002;24:302–316)

INTRODUCTION

Medication adherence has been defined as "the extent to which a person's behavior in terms of…taking medications…coincides with medical advice."[1] Nonadherence can lead to detrimental outcomes, including relapse of the disease being treated, nursing home admission, hospitalization,[2] and increased morbidity (eg, increase in relative risk of coronary heart disease[3]) and mortality. Conversely, increased adherence has the potential to improve treatment outcomes.

Haynes and coworkers[4] compiled a list of >250 factors that may affect patient adherence and classified these factors as modifiable or nonmodifiable. One nonmodifiable factor is the asymptomatic nature of a disease (eg, hypertension). Lack of symptoms is an insidious factor associated with patients' forgetting about or ignoring their disease condition. Drug regimen complexity, on the other hand, is a modifiable factor. It consists of 3 major components—the number of medications prescribed, daily dosing frequency, and complexity of administration (eg, parenteral vs oral). Hence, it may be possible to simplify the medication profile or reduce the dosing frequency to a minimum to enhance medication adherence.

The association between adherence to treatment and patient outcomes has been extensively investigated in the hypertensive population. Hershey and coworkers[5] demonstrated a positive correlation between adherence and blood pressure control, and Eisen et al[6] established adherence as a good predictor of blood pressure control. Sackett and colleagues[7] determined that an adherence level of ≥80% was necessary to decrease diastolic blood pressure in a systematic manner. Although the relationship between adherence and clinical outcome (eg, mortality) has not been directly established, the relationship between blood pressure control and mortality has been studied. Horwitz and Horwitz[8] reported a mortality rate of 1.4% for patients who were prescribed propranolol and took at least 75% of their medication, versus a rate of 4.2% for those who took <75% of their medication.

An initial survey of literature reviews of adherence to drug therapy failed to clearly identify the association between simplified dosing regimen and increased rate of adherence. Blackwell[9] cited 2 studies reporting negative effects of multiple daily dosing (MDD) on adherence, 2 studies reporting positive effects, and 2 studies reporting mixed effects. Haynes[10] reviewed several studies reporting a negative association between frequency of dosing and adherence, and 3 studies reporting no association. Reid[11] and Berg and colleagues[12] could not reach a definitive conclusion, based on reviews of published studies, that the simplification of a treatment regimen could improve adherence. Overall, reviews of the literature have failed to reach consensus on the association between adherence and daily dose frequency.

The present study used meta-analysis to examine the relationship between daily dosing frequency and patient adherence to antihypertensive drug therapy, and to assess whether a lower daily dose frequency is associated with higher adherence to antihypertensive pharmacotherapy. The specific study questions addressed were (Q1) whether once-daily, or QD, dosing is associated with higher adherence rates than MDD; (Q2) whether QD dosing is associated with higher adherence rates than BID dosing; and (Q3) whether BID dosing is associated with higher adherence rates than dosing >2 times daily (>BID).

METHODS

We searched the MEDLINE, Embase, and International Pharmaceutical Abstracts (IPA) databases for articles published in English or French between 1980 and 1998 using the key words *compliance, noncompliance, adherence, nonadherence, drug, drug therapy, drug treatment, hypertension, blood pressure,* and *study* or *trial.* A manual search was also performed on all references from retrieved articles and from review articles identified in the initial literature search, as well as textbooks on the topic.

We identified all primary studies that compared rates of adherence between different dosing frequencies of a drug regimen. We included any type of research design that involved a comparison, including prospective trials (eg, randomized controlled trials or cohort studies), retrospective chart reviews, and database analyses. Blinding/masking was not mandatory, but was noted. Any published study using an instrument to measure patient adherence was considered acceptable. However, studies must have used the same instrument to measure adherence in each comparison group and also have reported rates of adherence to chronically administered medications (ie, ≥10 weeks' duration) in solid, oral formulations (ie, tablets or capsules) to treat essential hypertension in adults ≥18 years of age.

Published abstracts or posters from symposia or colloquia were excluded. Also excluded were studies that dealt exclusively with very old patients (>74 years of age) since factors unrelated to dosing frequency (eg, memory loss or confusion experienced by many of these individuals[13]) could have influenced the findings. The inclusion criteria were kept stringent enough to capture comparative studies in the same therapeutic area and to avoid the possible introduction of bias from noncomparative trials or from trials comparing different therapeutic areas.

One investigator (M.I.) screened potential articles from the original search. Titles and abstracts were screened to determine eligibility. Potential articles were then masked by differential photocopying and by removing all identifiers such as names of authors, institutions, sponsors, and journals, as well as publication date. After training and practice to ensure interrater reliability, each paper was reviewed by 2 experienced judges (A.A. and N.M.), with disagreements settled by a third reviewer (A.L.I.). Evaluations of acceptability criteria were recorded on a checklist. Data were extracted from each selected article by 2 reviewers, who entered the data onto a collection form. Discrepancies were again arbitrated by the third reviewer.

For each eligible study, the effect size was calculated as the difference between adherence rates ($P_1 - P_2$), where P_1 was the proportion of adherent patients taking medication on 1 dosing regimen (eg, QD) and P_2 was the proportion using another regimen (eg, BID or MDD). Data were combined using a random-effects model as originally described by Cochran.[14]

Differences in rates of adherence were calculated between (1) QD dosing and MDD regimens, (2) QD and BID dosing regimens, and (3) BID dosing and >BID dosing regimens. In the primary analyses, adherence was defined as the proportion of patients who had taken ≥80% of doses. If this outcome measure was not available, the main adherence outcome as reported by the authors was used in the primary analysis.

All articles included in the meta-analysis were reviewed for characteristics such as publication year, study design, drug class, study duration, and adherence definition and measurement method. This examination was performed for further categorization of studies for subgroup analyses according to common characteristics. Subgroup analyses were performed, with subgroups identified a priori according to the following variables: method of measuring adherence, definition of adherence (ie, using 90% and 80% as minimum accepted rates[7]), study design (ie, prospective vs retrospective), medication class (eg, calcium channel blockers), and duration of treatment (ie, 3–6 months vs 12–24 months). Sensitivity analyses included reanalysis that excluded apparent outliers.

Homogeneity of effects was examined using a chi-square test. In addition, rates were plotted against each other to identify obvious outliers, as suggested by L'Abbé et al,[15] and regression analysis was used to confirm those observations, according to the method described by Tiku et al.[16]

The quality of the accepted articles was evaluated using a quality checklist adapted from Haynes et al.[4] The checklist examined 6 aspects of the article, including study design, selection and specification of the study sample, specification of the illness or condition, adherence measure used, description of the therapeutic regimen, and definition of adherence. The total possible score was 17 points; articles rated ≥8.5 (50%) were considered to be acceptable. Quality ratings were determined as for data extraction by 2 reviewers, with discrepancies arbitrated by the third reviewer.

RESULTS

An initial literature search yielded 871 potential articles. The investigators screened these articles by reading through their titles and abstracts to eliminate those that were obviously inappropriate for this research, and to compile a shorter list to be assessed for inclusion. This screening resulted in a list of 34 articles possibly containing pertinent information for the meta-analysis. Of these, a total of 8 articles[17–24] were selected in the review and selection process described previously.

Seven articles with 4669 observations (number of patients, doses, or other measure, as reported by authors) were used in the analysis of QD dosing versus MDD; 5 studies with 2152 observations were included in the analysis of QD versus BID dosing; and 4 articles with 7926 observations were used for the analysis of BID dosing versus >BID dosing. The respective numbers of observations were 1830 for QD dosing, 4405 for BID dosing, 4147 for >BID dosing, and 9655 for MDD, for an overall total of 11,485 observations.

Tables I and II summarize the major characteristics of the 8 selected articles, including sample sizes, reported adherence rates, definitions used for adherence, patient characteristics, study design, drug class, type of therapy, and adherence measurement methods.

Table I. Summary of studies included in the meta-analysis: Study characteristics.

Reference	Study Design	Drug Class(es)	Type of Therapy	Study Duration	Population Characteristics	Measurement Method
Baird et al, 1984[17]	Prospective	Beta-blockers	Monotherapy or with diuretic	10 weeks	Mean age 53 years, 52% male, hypertension duration 6 years	Pill count
Fujii and Seki, 1985[18]	Prospective	Various drugs including diuretics	50% monotherapy	Not indicated (patients in therapy for >1 year)	Mean age 56 years	Pill count and patient interview
Eisen et al, 1990[19]	Prospective	Various drugs	Not indicated	6 months	Median age 61 years, 83% black	Electronic compliance monitor
Halpern et al, 1993[20]	Retrospective	Potassium supplements	66% also taking diuretic	12 months	Mean age 58 years, 9% >80 years, 34% male	Prescription refill data
Hilleman et al, 1993[21]	Prospective	CCBs	Monotherapy	3 months	Mean age 50 years, 53% male, 12% also diabetic	Pill count
Farmer et al, 1994[22]	Retrospective	CCBs	Not indicated	2 years	Mean age 67 years, 46% male	Prescription refill data
Detry et al, 1995[23]	Prospective	CCBs	Not all monotherapy	12 weeks	Age <70 y, mean age 59 years	Pill count and MEMS
Boissel et al, 1996[24]	Prospective	CCBs	Not indicated	3 months	Mean age 61 years, 50% male	Patient interview

CCBs = calcium channel blockers; MEMS = medication event monitoring systems.

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