Effect of Medication Dosing Frequency on Adherence in Chronic Diseases

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Objective: To systematically review available data on the effect of daily medication dosing frequency on medication adherence in chronic disease states, as assessed by precise medication event monitoring systems (MEMS).

Study Design: Systematic review of relevant literature published between January 1986 and August 2007.

Methods: Four electronic databases were searched to identify appropriate studies. Study selection criteria included prospective study design, patient population with quiescent chronic disease, medication intervention prescribed to each treatment arm for at least 6 weeks, and the use of MEMS to measure adherence. Data were extracted on the chronic disease being treated, the frequency of medication dosing, and the proportion of days with correct number of doses.

Results: Twenty studies met the selection criteria. All studies reported higher adherence rates in patients using less frequently dosed medications, and these differences were statistically significant (P <.05) in 75% (15 of 20) of studies. For 5 of 6 studies comparing once-daily versus thrice-daily dosing, patients receiving once-daily dosing had 22% to 41% more adherent days compared with patients receiving thrice-daily dosing. For studies comparing once-daily versus twice-daily dosing, patients receiving once-daily dosing had 2% to 44% more adherent days compared with patients receiving twice-daily dosing, with most studies clustering around 13% to 26%.

Conclusion: Patients are more compliant with once-daily compared with twice-daily or thrice-daily treatment regimens.

(Am J Manag Care. 2009;15(6):e22-e33)

For author information and disclosures, see end of text.

According to the Centers for Disease Control and Prevention,[1] chronic diseases are the leading cause of morbidity and mortality in the United States today, accounting for 70% of all deaths. Unlike acute illnesses, chronic diseases frequently have long quiescent phases that may be punctuated by acute symptomatic flares (eg, ulcerative colitis and seizure disorders). Furthermore, patients with these conditions are often required to take 1 or more medications indefinitely for maintenance of quiescent disease. The combination of quiescent symptoms and need for long-term treatment may affect patients' daily use of these "maintenance" medications. Indeed, a prior study[2] demonstrated that patients with chronic diseases are likely to become less adherent with their medications over time. Adherence with maintenance medications has a direct effect on long-term outcomes and utilization of healthcare resources for patients with chronic disease.[3]

Adherence has been defined as the extent to which a patient acts in accordance with the prescribed interval and dose and dosing regimen.[4] Adherence is frequently quantified in the following 2 ways: (1) the proportion of days with correct number of doses consumed and (2) the proportion of correct number of doses taken (eg, for a thrice-daily dosing regimen, a patient could take medication twice every day, which would indicate that the patient took 67% of the correct number of doses, but have 0 days with correct number of doses taken). Adherence has been measured with many different techniques, including patient self-report, prescription refills, pill counts during follow-up visits, and measurement of blood levels of pharmaceuticals. However, previous findings indicate that medication event monitoring systems (MEMS) are more accurate than these various techniques at assessing medication adherence, presumably because these MEMS record the exact date and time of medication bottle openings via embedded microprocessor technology.[5,6]

Numerous investigations have studied the effect of different interventions on adherence, and simplification of medication dosing seems to be the single intervention with the strongest effect on adherence.[7] For many chronic diseases, the advent of extended-release pharmaceuticals has made simplification of medication dosing possible. A prior review explored the effect of medication dosing frequency on medication adherence almost a decade ago.[5] Although this review was an important addition to the literature, it had several

In this issue
Take-Away Points / e23
www.ajmc.com
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methodological shortcomings. Specifically, the patient population and intervention of interest were not well defined. As a result, heterogeneous patients were included such as those with acute symptomatic conditions and those with chronic asymptomatic conditions. Similarly, heterogeneous interventions were included such as oral, injected, and inhaled medications. Furthermore, explicit inclusion and exclusion criteria were not used. Finally, details of the individual included studies were not clearly presented, and an appraisal of the quality of these studies was not explicitly performed. Almost a decade has elapsed since this review was performed, a near eternity in the modern era of rapidly evolving medical science.[8]

Take-Away Points

Adherence to medical regimen is important in the optimal management of chronic diseases, and medication dosing frequency has important effects on medication adherence.

- Once-daily medical regimens result in up to twice as many adherent days as more frequent dosing regimens.
- When a choice is available, less frequently dosed medications should be considered in patients with chronic medical conditions.

The objective of this study was to perform a high-quality systematic review of studies comparing medication adherence rates between groups of patients taking medications with different daily dosing regimens. To minimize heterogeneity between studies and to maximize relevance to readers, we chose to focus our review on a specific important patient population (those with quiescent chronic disease conditions) being treated using a specific common route of medication administration (oral medications dosed 1-4 times daily). Because of the inherent inaccuracy of pill counts, patient self-reports, medication refill data, and measurement of blood levels, we elected to limit our search to studies using MEMS.[5,6] Through this review, we sought to systematically quantify the effect of daily dosing frequency of oral medications on adherence in quiescent (asymptomatic) chronic disease conditions.

METHODS

Search Strategy for Identification of Studies

Four electronic databases (MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, and the Cochrane Library) were searched from January 1986 (the year when MEMS were first introduced[9]) to August 2007 to identify potentially relevant articles published in the English language. The following terms were used for the primary search: (1a) Medical Subject Headings (MeSH) terms *patient compliance*; *treatment refusal*; *drug administration schedule*; *diabetes mellitus, type 2*; *dyslipidemias*; *hypertension*; *inflammatory bowel diseases*; *colitis, ulcerative*; *asthma*; *epilepsy*; and *seizures* (MEDLINE) or (1b) MeSH terms *patient compliance*, *drug dose regimen*, *non insulin dependent diabetes mellitus*, *dyslipidemia*, *dyslipoproteinemia*, *hyperlipidemia*, *hyperlipoproteinemia*, *hypertension*, *enteritis*, *ulcerative colitis*, *asthma*, *seizure*, *epilepsy*, and *convulsion* (EMBASE) and (2) in conjunction with the keywords *patient$*, *medication$*, *drug$*, *therapy*, *treatment*, *adhere$*, *comply*, *complian$*, *non?adhere$*, *non?complian$*, *schedule$*, *regime$*, *dos$*, *frequen$*, *diabet$*, *dyslipoproteinemi$*, *dyslipidemi$*, *hyperlipidem$*, *hypercholesterolem$*, *hypertensi$*, *high blood pressure*, *ulcerative colitis*, *asthma$*, *seizure$*, and *epilep$* (MEDLINE, EMBASE, and the Cochrane Library). Results from this initial query were limited to English-language controlled trials or systematic reviews. A manual recursive search of the references sections of systematic reviews was then performed to find other potentially relevant articles. The search strategy was designed and executed under the guidance of a trained medical information specialist (KK). Details of the search strategy are available in the **Appendix** to this Web exclusive article.

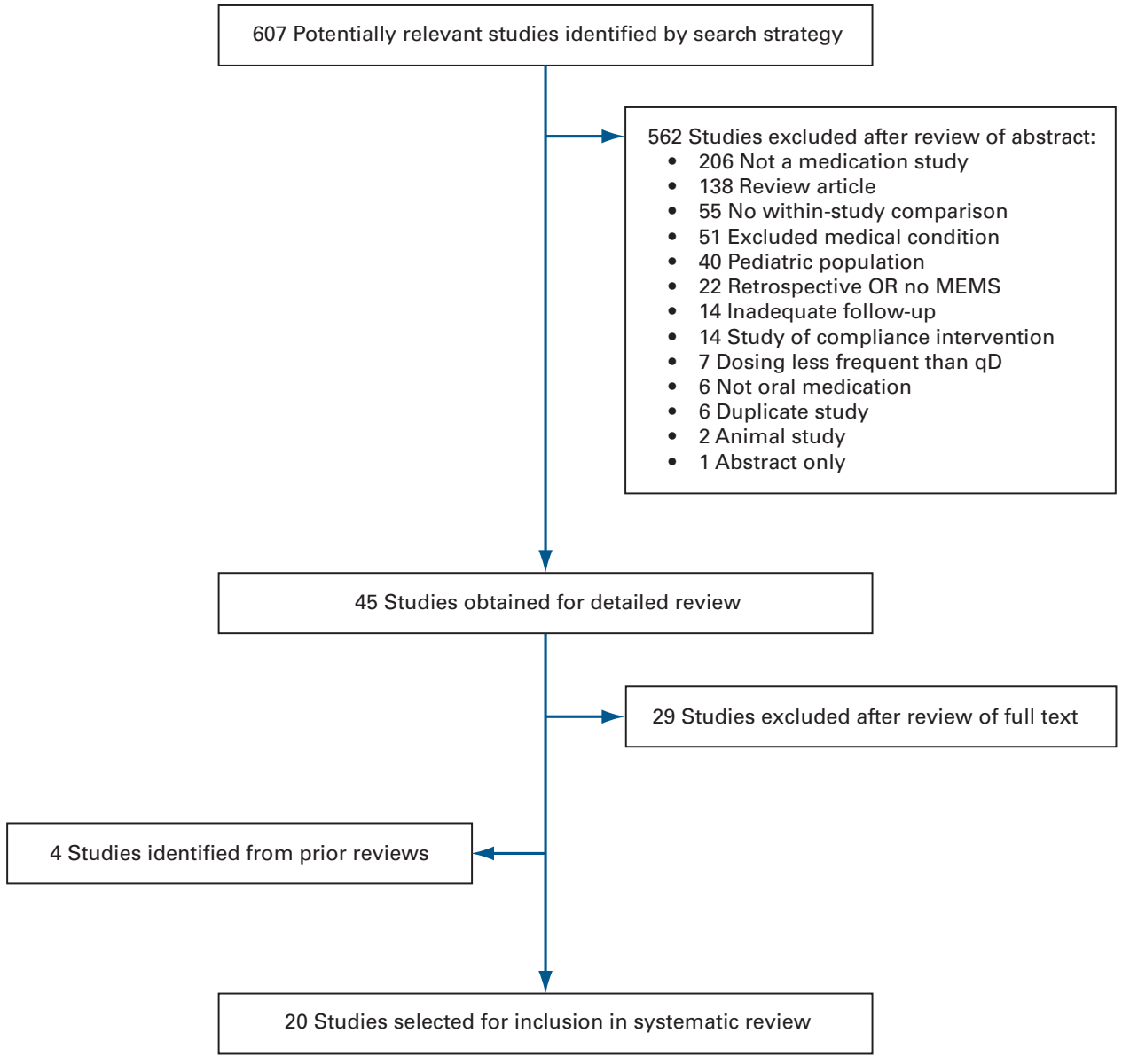
Study Selection Criteria

Abstracts of articles from the literature search were individually evaluated for possible inclusion in this study. Complete texts were obtained for articles that seemed potentially relevant. Studies meeting the following criteria were included: (1) English language; (2) full-article publication; (3) publication year 1986 to 2007; (4) prospective trial study design; (5) study population comprising adult patients with chronic diseases marked by quiescent asymptomatic periods, including hypertension, dyslipidemia, type 2 diabetes mellitus, asthma, seizure disorder, congestive heart failure, migraine headaches, and stable angina; (6) scheduled oral medication intervention administered 1 to 4 times daily; (7) adherence monitored via MEMS; (8) adherence rate results reported for each arm in the trial; and (9) patients followed up for at least 6 weeks. Studies enrolling patients with acute diseases, complex regimens of multiple medications taken multiple times per day (eg, for human immunodeficiency virus infection, cancer, or organ transplantation), or comorbid psychiatric conditions were excluded. Studies randomizing patients to 1 or more interventions specifically designed to enhance adherence were also excluded.

Data Extraction and Analysis

Eligible articles were independently reviewed by 2 of us (SDS and PS). Agreement between the investigators was higher than 95% for selection of articles to include in this review. Disagreement was resolved by consensus. Data were extracted on the following: (1) patient demographics, (2)

Figure 1. Flowchart Outlining Steps in Search Strategy



MEMS indicates medication event monitoring systems.

chronic disease being studied, (3) frequency of dosing regimens, and (4) patient adherence. Adherence was measured in the following 2 ways: (1) the proportion of days with correct number of bottle openings (doses consumed) under each dosing regimen (primary end point) and (2) the proportion of correct number of bottle openings over the course of the study (ie, the number of openings divided by the prescribed number of doses) (secondary end point). Data were extracted independently by the primary investigators, and disagreement on data extraction was resolved by consensus.

Because of differences in study design, study population, and data reporting, no attempt was made to combine these results into a meta-analysis. For the same reasons, no attempt was made to perform formal subgroup or sensitivity analyses. Results from individual studies are presented in tabular form with appropriate details about study design and populations, and adherence rates are discussed in the "Results" section.

RESULTS

Characteristics of Selected Studies

Six hundred seven references were identified by the search strategy outlined (Figure 1). Twenty studies[6,10-28] satisfied the primary selection criteria and were included in this

Table 1. Characteristics of 20 Included Studies

Source	Study Design	Disease State	Drug Class	Inclusion Criteria	Exclusion Criteria	Patients Blind to MEMS?
Andrejak et al,[10] 2000	Randomized	Hypertension	ACE inhibitors	Age, >18 y, diastolic hypertension	Serious chronic disease, kidney disease, dyskalemia, hypersensitivity or contraindication to ACE inhibitors; taking antihypertensive medication	No
Bohachick et al,[11] 2002	Cohort	Heart failure	ACE inhibitors	Age ≥21 y, taking ACE inhibitor, able to take own medications	Unstable medical condition, major psychiatric disorder, non–English speaking or reading	No
Brun,[12] 1994	Randomized	Stable angina	Nitrates	Stable angina	NR	No
Charpentier et al,[13] 2005	Randomized	Type 2 diabetes mellitus	Sulfonylureas	Type 2 diabetes mellitus, age 35-65 y, diabetes poorly controlled by diet or nonsulfonylurea drug	Severe chronic disease, BMI >40.0, kidney disease, allergy to sulfonylureas	No
Cramer et al,[14] 1995	Randomized	Epilepsy	Antiepileptics	Uncontrolled complex partial seizures, age 16-50 y	Poor intelligence (Wechsler Adult Intelligence Scale–Revised, <65), taking >2 antiepileptic drugs	No
Cramer et al,[15] 1989	Cohort	Epilepsy	Antiepileptics	Taking 1-2 antiepileptics	NR	No
Detry et al,[16] 1994	Cohort	Stable angina	Calcium channel blockers	Stable angina	Age ≥70 y, severe or uncontrolled hypertension, unstable angina, CHF, or liver failure	No
Eisen et al,[17] 1990	Randomized	Hypertension	Antihypertensives	History of hypertension; taking once-daily, twice-daily, or thrice-daily antihypertensive medication	NR	No
Girvin et al,[18] 1999	Randomized	Hypertension	ACE inhibitors	History of mild hypertension	Secondary hypertension or significant end-organ damage, pregnant or lactating, obesity (>125% ideal body weight), hypersensitivity or contraindication to ACE inhibitor, poor renal function or hyperkalemia, taking drugs that significantly alter blood pressure	No
Kardas et al,[21] 2004	Randomized	Stable angina	Nitrates	Age 40-75 y, stable angina, taking isosorbide mononitrate or dinitrate and no other nitrates	Unstable angina, NYHA class III-IV CHF, SBP <90 mm Hg, symptomatic infection, inability to administer medication alone	No

(Continued)

Table 1. Characteristics of 20 Included Studies *(Continued)*

Source	Study Design	Disease State	Drug Class	Inclusion Criteria	Exclusion Criteria	Patients Blind to MEMS?
Kardas,[19] 2005	Randomized	Type 2 diabetes mellitus	Sulfonylureas	Type 2 diabetes diagnosed ≤5 y before study, age 40-75 y, treated with diet and glibenclamide, BMI 22-30, glycosylated hemoglobin <9.0%	Type 1 diabetes mellitus, NYHA class III-IV CHF, unstable angina, symptomatic infection or peripheral vascular disease, inability to administer medication alone	No
Kardas,[20] 2007	Randomized	Stable angina	β-Blockers	Ischemic heart disease outpatients, Canadian Cardiovascular Society class I-II, age 40-75 y, β-blocker naive	Unstable angina, NYHA class III-IV CHF, SBP <90 mm Hg, or symptomatic infection; heart rate <60 beats/min and second- or third-degree atrioventricular block, inability to administer medication alone	No
Kruse and Weber,[23] 1990	Cohort	Various	Various	NR	Confusion, unable to open pill bottle	Yes[a]
Kruse et al,[22] 1994	Cohort	Hypertension	Calcium channel blocker and diuretic	Taking maintenance therapy for hypertension or starting treatment	NR	No
Lee et al,[6] 1996	Randomized	Hypertension	Various	African American, age 18-70 y, hypertension and kidney disease	NR	No
Leenen et al,[24] 1997	Randomized	Hypertension	Calcium channel blockers	Uncomplicated essential hypertension, age 18-80 y	Women of childbearing age, SBP >220 mm Hg, history of other cardiovascular disease, diabetes, kidney disease, or liver disease	No
Mulleners et al,[25] 1998	Cohort	Chronic migraines	Migraine prophylactics	Age 18-65 y, 2-8 migraines per mo	NR	Yes
Paes et al,[26] 1997	Cohort	Type 2 diabetes mellitus	Hypoglycemic agents	Type 2 diabetes mellitus	Insulin use, unable to obtain medications from pharmacy or use pill organizer	Yes
Rudd et al,[27] 1993	Cohort	Cardiovascular disease	Cardiovascular drugs	Chronic cardiovascular disease, 1-3 chronic oral cardiovascular drugs and ≤6 total medications	Not English-language literate	No
Winkler et al,[28] 2002	Unclear	Type 2 diabetes mellitus	Sulfonylureas	Type 2 diabetes mellitus	NR	No

ACE indicates angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; MEMS, medication event monitoring systems; NR, not reported; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Sixty-eight percent of patients were not informed about the purpose of the MEMS device.

review (Table 1 and Table 2). Of these 20 studies, 9 studies[10,11,13,18-21,25,28] (45%) were not included in the most recent prior systematic review[5] on this topic. The included studies covered various disease conditions, including hypertension (6 studies[6,10,17,18,22,24]), stable angina (4 studies[12,16,20,21]), type 2 diabetes mellitus (4 studies[13,19,26,28]), epilepsy (2 studies[14,15]), congestive heart failure (1 study[11]), migraine headaches (1 study[25]), and cardiovascular disease (1 study[27]), and 1 study[23] provided data on multiple different disease conditions. Eleven studies[6,10,12-14,17-21,24] were randomized, 8 were observational (cohort) studies,[11,15,16,22,23,25-27] and 1 study[28] did not adequately specify the study design used. Two studies[25,26] did not inform any enrolled patients about the purpose of the MEMS, and 1 study[23] informed only 32% of participating patients about the purpose of the device. Study size varied from 19 to 250 patients, and follow-up was excellent (>90%) for most studies (Table 2). The mean duration of follow-up varied from 42 to 214 days, with 12 studies (60%) following up patients for at least 90 days and 4 studies (20%) following up patients for at least 180 days. Eighteen studies reported adherence data for the primary end point (proportion of days with correct number of bottle openings) on once-daily dosing, 17 reported on twice-daily dosing, 7 reported on thrice-daily dosing, and 2 reported on dosing 4 times a day. Two studies combined twice-daily and thrice-daily adherence data. Most studies used Wilcoxon rank sum test (also known as Mann-Whitney test), *t* test, or analysis of variance to compare adherence rates between treatment arms, although the statistical test used could not be determined from the published articles in 6 studies. Results are graphically presented for studies of once-daily versus thrice-daily dosing in Figure 2.

Characteristics of Studies on Each Chronic Disease

Hypertension. Six included studies[6,10,17,18,22,24] investigated the effect of dosing frequency of various antihypertensive medications. Two of these studies enrolled fewer than 30 patients, and 2 enrolled more than 150 patients. All but 1 of these studies randomized patients to a treatment arm. Only 1 study[17] reported data for once-daily versus thrice-daily dosing (84% vs 59% adherence; $P < .05$). No studies reported data for dosing 4 times a day. For once-daily dosing regimens, the adherence rate (proportion of days with correct number of bottle openings) ranged from 49% to 94%.[6,10,17,18,22,24] The adherence rate for twice-daily regimens ranged from 5% to 82%.[6,10,17,18,22,24] The lower end of the range for both dosing regimens was markedly skewed by a single outlier study.[6] This trial reported adherence data as the number of doses taken at the prescribed time rather than on the prescribed day, leading to much lower measured adherence than in the other trials. The within-study differences in adherence for once-daily versus twice-daily dosing regimens ranged from 5% to 44%, with 4 studies[6,10,18,24] of 6 reporting the differences to be statistically significant.

Stable Angina. Four included studies[12,16,20,21] investigated the effect of dosing frequency of various antianginal medications. All but 1 of these studies were randomized, and all but 1 enrolled at least 100 patients. All studies compared once-daily with twice-daily dosing. Once-daily dosing adherence ranged from 84% to 97%, and twice-daily dosing adherence ranged from 59% to 88%. The within-study differences in adherence for once-daily versus twice-daily dosing regimens ranged from 9% to 26%, with all studies reporting the differences to be statistically significant.

Type 2 Diabetes Mellitus. Four included studies[13,19,26,28] investigated the effect of dosing frequency of various oral diabetes medications. All studies reported data on once-daily and twice-daily adherence. Three studies[13,26,28] reported data on thrice-daily adherence also, although 2 studies[13,28] combined results for twice-daily and thrice-daily dosing. For once-daily dosing, adherence ranged from 79% to 94%. For twice-daily or thrice-daily dosing, the adherence rate ranged from 38% to 67%. The within-study differences in adherence for once-daily versus twice-daily or thrice-daily dosing regimens ranged from 13% to 41%, with all studies reporting the differences across regimens to be statistically significant.

Other Chronic Diseases. The 6 remaining studies[11,14,15,23,25,27] investigated the effect of various medications for seizure disorder, congestive heart failure, migraine headaches, and other chronic conditions. One of these trials was randomized, and the remaining studies were observational only. Data were reported for the following dosing regimens: once daily (4 studies[11,15,23,25]), twice daily (5 studies[11,14,15,23,25]), thrice daily (5 studies[11,14,15,23,25]), and dosing 4 times a day (2 studies[14,15]). Adherence for once-daily, twice-daily, and thrice-daily regimens ranged from 77% to 90%, 60% to 86%, and 50% to 80%, respectively. The single study evaluating dosing 4 times a day reported an adherence rate of 39%. Of studies reporting once-daily and twice-daily adherence, the within-study adherence differences ranged from 2% to 20%, with 1 of 4 studies reporting the difference to be statistically significant. Of studies reporting once-daily and thrice-daily adherence, the within-study adherence differences ranged from 10% to 38%, with 1 of 4 studies reporting the difference to be statistically significant.

DISCUSSION

The bulk of disease burden in the United States is attributable to chronic health conditions, many of which require

Table 2. Adherence Data From 20 Included Studies

Source	No. Enrolled	% Analyzed	Mean Follow-Up, d	Age, Mean (SD), y	% Male	Statistical Test Used
Andrejak et al,[10] 2000	162	82	183	57 (?)	45	Wilcoxon rank sum
Bohachick et al,[11] 2002	250	68	~90	55 (12)	70	Wilcoxon rank sum
Brun,[12] 1994	31	100	79	63 (?)	65	Wilcoxon rank sum
Charpentier et al,[13] 2005	233	86	189	55 (7)	60	*t* Test[c]
Cramer et al,[14] 1995	111	59	189	NR	NR	None
Cramer et al,[15] 1989	24	100	132	NR	50	*t* Test
Detry et al,[16] 1994	124	84	~84	61 (?)	69	Unclear
Eisen et al,[17] 1990	192[d]	55	147	61 (?)[e]	100	*t* Test
Girvin et al,[18] 1999	27	93	~112	62 (?)	64	*t* Test
Kardas et al,[21] 2004	101	99	63	64 (?)	41	*t* Test
Kardas,[19] 2005	105	92	122	62 (?)	46	*t* Test
Kardas,[20] 2007	112	86	66	57 (10)	41	Wilcoxon rank sum
Kruse and Weber,[23] 1990	31	97	42	50 (?)	57	Unclear
Kruse et al,[22] 1994	24	100	214	62 (?)	54	Unclear
Lee et al,[6] 1996	94	97	138	53 (11)	76	ANOVA
Leenen et al,[24] 1997	198	93	~140	55 (14)	62	Unclear
Mulleners et al,[25] 1998	38	76	~56	NR	24	ANOVA
Paes et al,[26] 1997	91	100	155	69 (11)	40	ANOVA
Rudd et al,[27] 1993	33	100	84	56 (2)	64	Unclear
Winkler et al,[28] 2002	19	100	54	69 (11)	68	Unclear

ANOVA indicates analysis of variance; NR, not reported.
[a]Difference statistically significant ($P < .05$).
[b]Proportion of patients taking dose during prescribed dosing period.
[c]*t* Test was performed by us using the mean (SD) reported in the published text.
[d]Some patients received feedback to enhance compliance but could not be excluded from analysis.
[e]Median age (not mean).
[f]Proportion of patients taking a mean (SD) of at least 80% (25%) of medications at prescribed time.

long-term medication for optimal management.[1] Adherence to medication regimens has an important role in response to therapy and in maintenance of disease quiescence.[3] As a result, medication dosing frequency has been the subject of numerous trials on medication adherence. Our review, the first (to our knowledge) in almost 10 years on this topic, suggests that medication dosing frequency is associated with medication adherence, with less frequent dosing resulting in better adherence. For 5 studies[11,17,23,25,26] of 6 comparing once-daily versus thrice-daily dosing, patients receiving once-daily dosing had 22% to 41% more adherent days compared with patients receiving thrice-daily dosing. For most studies comparing once-daily versus twice-daily dosing, patients receiving once-daily dosing had 13% to 26% more adherent days compared with patients receiving twice-daily dosing.[6,10,16,18-21,25,26] Our review also demonstrates that there are no medication adherence data using MEMS for many chronic diseases frequently characterized by long quiescent phases punctuated by acute symptomatic flares such as ulcerative colitis.

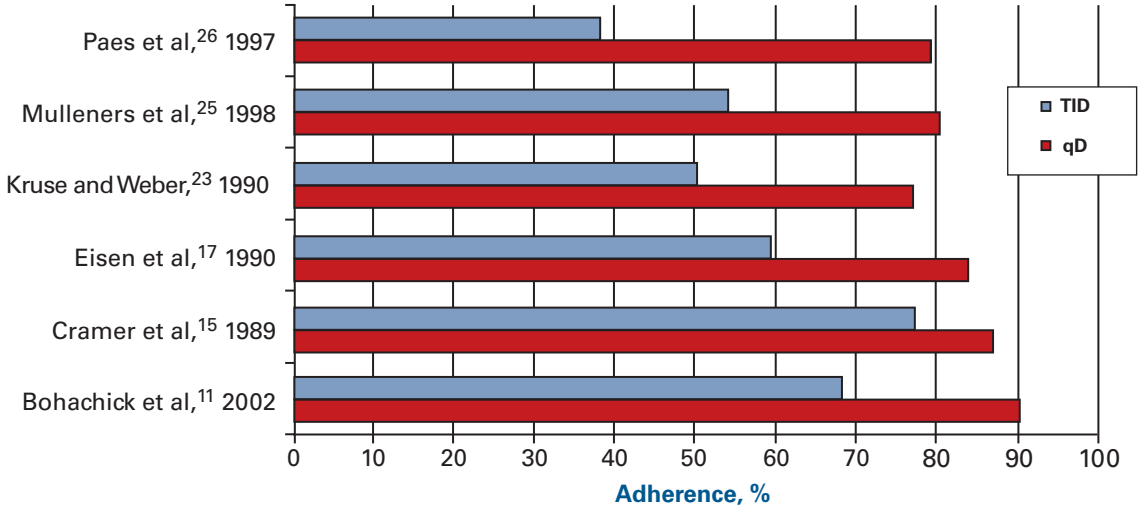
Several studies have recently evaluated this topic using various methods and have demonstrated that lower dosing frequency leads to increased medication adherence. The first systematic review on the association between medication dosing frequency and adherence was published by Claxton and colleagues[5] in 2001. Their results demonstrated that patients who were prescribed more frequent dosing regimens were less likely to adhere to their medication regimens, with a mean (SD) dose-taking compliance of 79% (14%) with once-daily dosing, 69% (15%) with twice-daily dosing, and 65% (16%) with thrice-daily dosing. However, these authors included various acute and chronic medical conditions requiring oral, inhaled, and injected therapies in their review

% Total Correct Openings				% Days With Correct Openings			
Once Daily	Twice Daily	Thrice Daily	4 Times a Day	Once Daily	Twice Daily	Thrice Daily	4 Times a Day
99[a]	97	—	—	94[a,b]	78	—	—
98[a]	93	89	—	90[a]	84	68	—
99	95	—	—	97[a]	88	—	—
—	—	—	—	87[a]	67	67	—
—	—	—	—	—	86	80	80
—	—	—	—	87	81	77	39[a]
96	91	—	—	85[a]	71	—	—
96	93	84[a]	—	84	75	59[a]	—
100[a]	90	—	—	92[a]	73	—	—
89[a]	74	—	—	85[a]	59	—	—
93[a]	87	—	—	86[a]	67	—	—
86[a]	76	—	—	84[a]	64	—	—
77	86	86	77	75	—	50	—
89	88	—	—	85	80	—	—
—	—	—	—	49[f]	5	—	—
94	91	—	—	90[a]	82	—	—
—	—	—	—	80	60	54	—
99[a]	83	66	—	79[a]	66	38	—
82	76	72	—	—	—	—	—
100	81[a]	81[a]	—	94	58[a]	58[a]	—

of studies published from 1986 to 2000, and the lack of strict inclusion and exclusion criteria led to significant heterogeneity in their results. A subsequent study[3] in 2003 about the effect of dosing frequency on health outcomes reported data on both prospective and retrospective studies of dosing frequency and adherence. The authors concluded that adherence with maintenance medications has a direct effect on long-term outcomes and on utilization of healthcare resources for patients with chronic disease. Nevertheless, they included retrospective studies and studies that did not use an electronic monitoring device, suggesting the possibility of imprecise adherence measurements. Finally, a study by Wetzels and colleagues[29] reviewed the literature on the effect of dosing regimens of antihypertensive agents on blood pressure control. This study excluded investigations not using MEMS and identified 33 relevant articles. The authors concluded that dosing frequency affects adherence. However, 17 of the included articles had short follow-up, lack of a within-study comparison group, or lack of appropriate adherence data. Our review is the first (to our knowledge) since the study by Claxton and colleagues[5] to specifically address the question of how dosing frequency affects medication adherence. Unlike Claxton and colleagues, we limited our review to studies of oral medication use in asymptomatic chronic disease states not requiring complex medical regimens. Our results should help reinforce the notion that simplification of drug dosing can improve medication adherence, likely affecting outcomes and healthcare utilization in a subset of patients.

Our study also highlights the many limitations of the existing literature on this topic. First, investigations varied considerably in study design and in inclusion and exclusion criteria. With different methods and patient populations,

Figure 2. Adherence Rates in Studies Comparing Once-Daily (qD) With Thrice-Daily (TID) Dosing Regimens



results cannot be directly compared between studies. Second, many included studies with small numbers of patients, making it difficult to draw statistical inferences from the results. In addition, some of these small studies purported to randomize patients to 1 or more treatment arms. However, the effectiveness of randomization is greatly limited by such small sample sizes. Third, there are few data on adherence to more frequent dosing regimens such as thrice-daily or dosing 4 times a day. There continues to be no generally agreed-on measure of adherence, and future studies on this topic should ideally be randomized and sufficiently powered and use agreed-on end points for measuring adherence. Fourth, although MEMS is the most objective available tool for quantifying medication adherence, it too has its limitations. Specifically, MEMS equates pill container opening with pill taking, and scenarios exist where container opening and pill taking may not be equivalent (such as patients removing multiple pills at 1 opening for later consumption or opening and closing the container without removing pills).[15,30]

Our study also has several strengths that should be highlighted. First, we present the most recent systematic review (to our knowledge) since 2001 on this important topic. Findings from a recent study[8] suggested that systematic reviews should be updated at least every 5 years because of continually emerging data that can change overall conclusions, and our review identified numerous important new articles on this topic that were not included in previous studies. Second, we used a comprehensive search strategy developed and implemented with the assistance of a trained medical information specialist. Third, we focused our search on a specific population, namely, patients with minimally symptomatic chronic conditions taking oral medications. As a result, our data are qualitatively less heterogeneous than those presented in the prior review[5] on this topic.

In summary, published data demonstrate that less frequent dosing of medications in patients with a chronic disease improves medication adherence in once-daily versus twice-daily dosing and in once-daily versus thrice-daily dosing. Previous evidence demonstrates that improved adherence improves long-term outcomes and reduces healthcare utilization for many chronic disease states. When possible, physicians treating patients with a chronic disease should strongly consider prescribing medications requiring less frequent dosing. Future studies should be performed to address this topic for other chronic disorders characterized by long quiescent phases punctuated by acute flares, and these studies should use MEMS technology to assess adherence and a rigorous study design, adequate power, and agreed-on end points for measuring adherence.

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Funding Source: None reported.

Author Disclosure: Dr Schoenfeld reports receiving honoraria from Shire Pharmaceuticals for work as a consultant in his role as a partner in MD Evidence, LLC. Dr Dubinsky reports that she is a paid consultant for Shire Pharmaceuticals. The other authors (SDS, KK) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (SDS, PS); acquisition of data (SDS, PS, KK, MCD); analysis and interpretation of data (SDS, PS, MCD); drafting of the manuscript (SDS, PS); critical revision of the manuscript for important intellectual content (SDS, PS, KK, MCD); statistical analysis (SDS, PS); provision of study materials or patients (SDS); obtaining funding (PS); and administrative, technical, or logistic support (KK).

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Appendix. Search Strategy

Search date: September 4, 2007
Databases searched: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library

Database: Ovid MEDLINE(R) <1950 to August Week 4 2007>
Search Strategy:

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1 exp Diabetes Mellitus, Type 2/ (45357)
2 diabet$.mp. (284636)
3 exp Dyslipidemias/ (47363)
4 (dyslipoproteinemi$ or dyslipidemi$ or Hyperlipidem$ or hypercholesterolem$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (53005)
5 exp Hypertension/ (165755)
6 (hypertensi$ or high blood pressure).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (272862)
7 exp inflammatory bowel diseases/ or exp colitis, ulcerative/ (41600)
8 (ulcerative adj1 colitis).mp. (24455)
9 exp Asthma/ or asthma$.mp. (98309)
10 exp Epilepsy/ or exp Seizures/ (98119)
11 (seizure$ or epilep$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (121119)
12 or/1-11 (822382)
13 exp Patient Compliance/ or exp Treatment Refusal/ (39809)
14 (adhere$ or comply or complian$ or non?adhere$ or non?complian$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (151637)
15 13 or 14 (158193)
16 exp Drug Administration Schedule/ (61977)
17 ((drug$ or medication$ or medicine$ or dos$) adj2 (frequen$ or schedule$ or regime$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (88600)
18 16 or 17 (89199)
19 12 and 15 and 18 (1003)
20 limit 19 to (humans and english language and yr="1986 - 2007") (786)
21 limit 20 to (controlled clinical trial or meta analysis or randomized controlled trial) (194)
22 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (63844)
23 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (506928)
24 exp Double-Blind Method/ (92958)
25 exp Control Groups/ (788)
26 exp Placebos/ (26462)
27 RCT.mp. (2361)
28 or/21-27 (578906)
29 20 and 28 (276)

■ **Appendix.** Search Strategy *(Continued)*

Database: EMBASE <1980 to 2007 Week 35>

Search Strategy:

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1 exp Non Insulin Dependent Diabetes Mellitus/ (47862)
2 diabet$.mp. (244548)
3 exp dyslipidemia/ or exp dyslipoproteinemia/ or exp hyperlipidemia/ or exp hyperlipoproteinemia/ (59504)
4 (dyslipoproteinemi$ or dyslipidemi$ or Hyperlipidem$ or hypercholesterolem$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (57802)
5 exp HYPERTENSION/ (215879)
6 (hypertensi$ or high blood pressure).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (254025)
7 exp enteritis/ or exp ulcerative colitis/ (71602)
8 (ulcerative adj1 colitis).mp. (19221)
9 asthma$.mp. or exp ASTHMA/ (90655)
10 exp "Seizure, Epilepsy and Convulsion"/ (113883)
11 ((seizure$ adj2 disorder$) or epilep$).mp. (71276)
12 or/1-11 (764254)
13 exp Patient Compliance/ (39643)
14 (adhere$ or comply or complian$ or non?adhere$ or non?complian$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (140703)
15 exp Drug Dose Regimen/ (19556)
16 ((drug$ or medication$ or dos$) adj2 (frequen$ or schedule$ or regime$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (50291)
17 13 or 14 (140703)
18 15 or 16 (50291)
19 12 and 17 and 18 (1129)
20 limit 19 to (human and english language and yr="1986 - 2007") (959)
21 Randomized Controlled Trial/ (146648)
22 (random$ or RCT$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (382726)
23 exp Randomization/ (23723)
24 exp Random Sample/ (756)
25 Double Blind Procedure/ (65699)
26 exp Triple Blind Procedure/ (8)
27 exp Control Group/ (951)
28 exp PLACEBO/ (103122)
29 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).ti,ab. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (51798)
30 or/21-29 (489289)
31 20 and 30 (333)