SUBJECT REVIEW

Dosing Frequency and Medication Adherence in Chronic Disease

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ABSTRACT

BACKGROUND: Prior research has shown a decrease in medication adherence as dosing frequency increases; however, meta-analyses have not been able to demonstrate a significant inverse relationship between dosing frequency and adherence when comparing twice-daily versus once-daily dosing.

OBJECTIVE: To determine the effect of scheduled dosing frequency on medication adherence in patients with chronic diseases.

METHODS: A systematic literature search of MEDLINE and Embase from January 1986 to December 2011 and a hand search of references were performed to identify eligible studies. Randomized and observational studies were included if they utilized a prospective design, assessed adult patients with chronic diseases, evaluated scheduled oral medications taken 1 to 4 times daily, and measured medication adherence for at least 1 month using an electronic monitoring device. Manual searches of reference sections of identified studies and systematic reviews were also performed to find other potentially relevant articles. Standard definitions for medication taking, regimen, and timing adherence were used and evaluated. Studies were pooled using a multivariate linear mixed-model method to conduct meta-regression accounting for both random and fixed effects, weighted by the inverse of the variance of medication adherence.

RESULTS: Fifty-one studies, comprising 65, 76, and 47 dosing frequency arms for the taking, regimen, and timing adherence endpoints were included. Unadjusted adherence estimates were highest when the least stringent definition, taking adherence, was used (range for dosing frequencies: 80.1%-93.0%) and lowest when the most stringent definition, timing adherence, was used (range for dosing frequencies: 18.8%-76.9%). In multivariate meta-regression analyses, the adjusted weighted mean percentage adherence rates for all regimens dosed more frequently than once per day were significantly lower compared with once-daily regimens (for 2-times, 3-times, and 4-times daily regimens, respectively: differences for taking adherence: –6.7%, –13.5%, and –19.2%; regimen adherence: –13.1%, –24.9%, and –23.1%; and timing adherence: –26.7%, –39.0%, and –54.2%).

CONCLUSION: Patients with chronic diseases appear to be more adherent with once-daily compared with more frequently scheduled medication regimens. The use of more stringent definitions of adherence magnified these findings.

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What is already known about this subject

- Many chronic diseases require that patients take 1 or more maintenance medications, often taken more than once daily. Medication nonadherence is associated with suboptimal health outcomes and increased health care costs. Previous research suggests that a substantial inverse relationship between dosing frequency and medication adherence may exist; however, differences between once- and twice-daily regimens or twice- and 3-times daily regimens have not been demonstrated.
- An outdated meta-analysis by Claxton et al. (2001) explored the effect of medication dosing frequency on medication adherence, including studies published through the year 2000. Its limitations stem from a suboptimal statistical meta-analytic technique, averaging the mean adherence rates for the included studies, as well as from including a highly heterogeneous group of acute and chronic disease studies utilizing various dosage forms. While this meta-analysis showed higher adherence for once-daily dosing compared with 3- or 4-times daily dosing, it did not show a difference between once- and twice-daily dosing.
- No meta-analysis has demonstrated a significant inverse relationship between dosing frequency and medication adherence when comparing once- and twice-daily dosing.

What this study adds

- The present study employed a methodologically sound analysis utilizing a multivariate linear mixed-model method to conduct meta-regression accounting for both random and fixed effects, weighted by the inverse of the variance of medication adherence. Fixed effects were assumed for study-level factors, including dosing frequency, disease state, study design, country in which study was conducted, participant's awareness of electronic monitoring, duration of adherence monitoring, and year of publication.
- In multivariate meta-regression analyses, the adjusted weighted mean percentage adherence rates for twice-daily, 3-times daily, and 4-times daily dosing regimens, respectively, were significantly lower compared with once-daily regimens (differences for taking adherence: –6.7%, –13.5%, –19.2%; regimen adherence: –13.1%, –24.9%, –23.1%; and timing adherence: –26.7%, –39.0%, –54.2%). Using the more stringent definition of timing adherence, differences between once-daily and multiple doses were magnified.

Chronic disease is the primary cause of morbidity and mortality in the United States.[1] Many chronic diseases require patients to take 1 or more maintenance medications, often more than once daily. Prior research suggests that an inverse relationship between dosing frequency and medication adherence may exist.[2,3]

In 2009, Siani et al. published a systematic review that included specific quiescent chronic disease states: hypertension, dyslipidemia, type 2 diabetes mellitus, asthma, seizure disorder, congestive heart failure, migraine headaches, and stable angina.[2] Twenty studies published through August 2007 were included, but the authors did not attempt to statistically pool data from these studies. The results of included studies were generally favorable for less frequent dosing regimens, with 15 of 20 studies showing a statistically significant inverse relationship between dosing frequency and adherence. However, the authors noted that there are few data on adherence to more frequent dosing regimens (3- and 4-times daily), and most included studies had small sample sizes, making it extremely challenging to draw any statistical conclusions. In addition, higher dosing frequencies such as 3-times daily and 4-times daily were reported only in a few identified studies.[2]

An outdated meta-analysis by Claxton et al. (2001) explored the effect of medication dosing frequency on medication adherence including studies published up to the year 2000; however, the researchers averaged the mean adherence rates of all the included studies rather than using proper meta-analytic techniques.[3] Moreover, Claxton et al. pooled a heterogeneous group of studies, including those examining adherence in acute and chronic conditions and evaluating oral, injectable, and inhaled medications, without adjusting for these confounders.[4] While the analysis found adherence to be significantly higher for once-daily dosing compared with 3- or 4-times daily dosing, it did not demonstrate a statistically significant difference in adherence between once- and twice-daily regimens.[3] With the inclusion of studies published in the last decade as well as the use of stronger meta-analytic techniques, it seems prudent to re-explore the relationship between dosing frequency and medication adherence.

The primary objective of the current study was to conduct a methodologically sound systematic review and meta-regression analysis to evaluate the association of scheduled medication dosing frequency (1 to 4 times daily) with medication adherence in patients with chronic diseases.

Methods

Study Identification

We conducted a literature search in the bibliographic databases MEDLINE and Embase from 1986 (the year the first electronic medication monitoring device became available) through December 2011 using the search strategies detailed in the Appendix. We limited the results of this search to controlled trials or systematic reviews published in English. Manual searches of reference sections of included studies as well as systematic reviews were performed to identify other potentially relevant articles.

Medication adherence can be measured through various means, including patient self-report, analysis of prescription refill records, measurement of serum drug levels, pill counts, and electronic monitors, such as medication event monitoring systems (MEMS; manufactured by AARDEX Group Ltd., Sion, Switzerland).[5] No one method is without limitation; however, electronic monitors are commonly considered to provide the most accurate information for measuring adherence. These electronic devices are capable of taking into account both the number and time of pill container openings, allowing noninvasive assessment of more complex adherence definitions such as taking adherence and regimen adherence. For this reason, the search was limited to studies monitoring adherence via electronic monitoring methods. In order to find other potentially relevant articles, we manually searched the reference sections of included studies and systematic reviews as well as bibliographies obtained from the AARDEX website (http://www.aardex-group.com and http://www.iadherence.org/publication.adx).

Study Selection

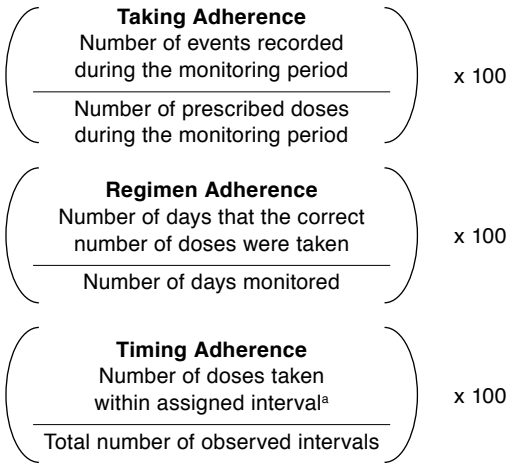
The following inclusion criteria were applied to identified articles: (a) prospective study design or systematic review with or without meta-analysis, (b) adult patient population with 1 or more chronic diseases, (c) scheduled oral medication intervention to be taken 1 to 4 times daily, (d) follow-up for 1 or more months, and (e) electronic monitoring of adherence reported. For studies that randomized patients to 1 or more interventions specifically designed to enhance adherence (other than electronic monitoring itself), only the control arms were included. An *a priori* decision to exclude studies that evaluated human immunodeficiency virus (HIV), psychiatric illness, cancer, or treatment to prevent organ rejection was made because medication adherence in these populations is not likely representative of the average chronic disease population.

Data Extraction

Identified articles were independently reviewed by 2 investigators (Roberts and Sobieraj) with disagreements resolved by a third (Coleman). The following data were extracted from each of the 51 included studies: (a) patient demographics, (b) study design, (c) country in which study was conducted, (d) chronic disease being studied, (e) whether patients were blinded to electronic monitoring, (f) frequency of dosing regimens, (g) duration of follow-up, and (h) patient adherence data. When necessary, authors were contacted via e-mail for clarification or additional data.

Three definitions commonly reported in the literature were used to measure adherence: taking, regimen, and timing

FIGURE 1 *Calculation of 3 Adherence Measures*



[a]*Assigned intervals varied among studies.*

adherence (Figure 1).[2,3,6] Taking adherence was defined as the number of openings divided by the prescribed number of doses. Regimen adherence was defined as the percentage of days with the appropriate number of doses taken, putting importance on the correct number of cap openings per day (and not allowing extra cap openings on one day to compensate for missed openings on another day). Timing adherence, the most stringent definition of adherence commonly used in the medical literature, was defined as the percentage of doses taken within assigned intervals. This latter adherence definition may be particularly important for drugs that should be administered at specific times of day for pharmacokinetic reasons (e.g., those that should or should not be administered with meals due to effects on bioavailability); to improve tolerability (e.g., thiazides should not administered before bedtime to prevent frequent waking to urinate); or to maintain efficacy (e.g., administering nitrates on a schedule that assures a nitrate-free interval and maintaining continuous dopaminergic stimulation and modulating end-of-dose failure with levodopa in Parkinson's disease).[3,7-9]

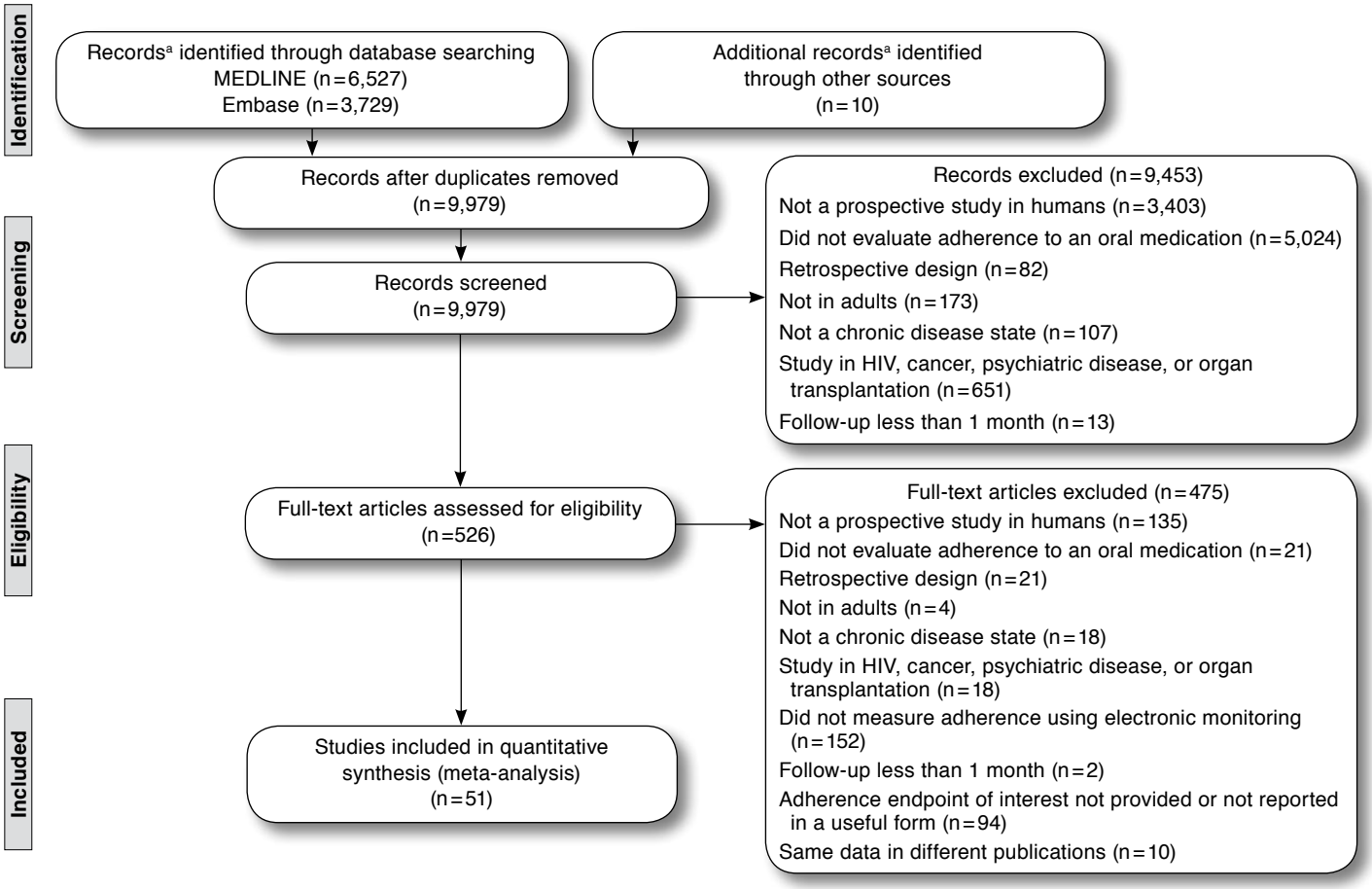
Data Synthesis

Individual arms from included studies were categorized into the 4 dosing frequencies evaluated (1 to 4 times daily) and pooled using meta-analytic methods within each frequency. In order to determine how each dosing frequency as well as other pertinent study characteristics were associated with medication adherence, both traditional random-effects meta-analyses and meta-regression analyses were conducted. A multivariate linear mixed-model method was used to conduct meta-regression accounting for both random and fixed effects.[4] Fixed effects were assumed for study-level factors, including dosing frequency, disease state, study design, country in which study was conducted, participant's awareness of electronic monitoring, duration of adherence monitoring, and year of publication. Both the traditional meta-analyses and the multivariate analyses were weighted by the inverse of the variance of medication adherence. Statistical analysis was performed using StatsDirect version 2.7.6 (StatsDirect Ltd., Cheshire, England) and SAS (PROC MIXED), version 9.1 (SAS Institute Inc., Cary, NC).

Results

The initial systematic literature search yielded 9,979 nonduplicate citations (Figure 2), and after screening, 526 of these citations were reviewed at the full-text level. Of these, 475 were excluded for various reasons, most commonly because the publication was not a report of a prospective study in humans or did not measure adherence using an electronic monitoring device. A total of 51 unique studies were identified for inclusion (Table 1).[6,10-59] From these, 65, 76, and 47 separate dosing frequency arms were available for the taking, regimen, and timing adherence endpoints, respectively (Table 2). Included studies were published between 1987 and 2011, with approximately one-half (n = 25) published in the last decade. The studies enrolled between 4 and 501 patients and followed them for no less than 28 days and up to 365 days; 20% of studies (n = 10) followed patients for 168 days (six 28-day periods) or more. Only 15.7% of study reports (n = 8) explicitly stated that they blinded patients to the electronic monitoring device. Nineteen of the 51 studies (37.3%) were conducted in the United States, with the remainder conducted in various European countries. A majority (29 of 51) of studies were conducted in patient populations with cardiovascular diseases (most commonly hypertension but also hyperlipidemia, heart failure, stable angina, and anticoagulation). Other disease states included neurologic (epilepsy, migraine, and Parkinson's disease), type 2 diabetes mellitus (T2DM), asthma, and other/mixed (psoriasis, vitamin deficiency, osteoporosis, autoimmune disease, and gout). Drugs monitored were either specific therapies (e.g., warfarin for anticoagulation), pharmacologic classes (e.g., beta-blockers for heart failure), or broader categories (e.g., antihypertensive agents, anti-Parkinson's drugs). With the exception of epilepsy and asthma studies, which enrolled younger adults, the mean/median age of study populations was between 50 and 70 years. In most studies, the proportions of men and women were approximately equal, except for 1 study enrolling only women with osteopenia and 4 studies that enrolled only men (studies of hypertension [n = 2], T2DM [n = 1], and hyperlipidemia [n = 1]). All studies collected adherence data prospectively, with 8 studies randomizing patients according to dosing frequency, 17 studies presenting a *post hoc* observational analysis of randomized data, and the remaining 26 using an observational study design.

FIGURE 2 *Flow Diagram for Study Inclusion*



[a]Records include titles and full abstracts; abstracts were not available for all titles.
HIV = human immunodeficiency virus.

In traditional random-effects meta-analysis of each of the 3 adherence definitions, weighted mean adherence rates were notably lower for regimens taken more than once per day than for once-daily regimens (Table 3). Unadjusted adherence rates were highest when taking adherence, the least stringent measure, was evaluated (range for dosing frequencies: 80.1% to 93.0%) and lowest when timing adherence, the most stringent, was evaluated (range for dosing frequencies: 18.8% to 76.9%).

Upon adjustment using multivariate meta-regression, these findings remained consistent and were statistically significant (Table 4). The adjusted differences in adherence across frequencies (once daily vs. others) were again most profound when evaluating timing adherence, followed by regimen and taking adherence. Compared with once-daily regimens (n = 2,006 patients), taking adherence was 6.7%, 13.5%, and 19.2% lower in twice- (n = 1,259), 3-times (n = 362), and 4-times (n = 57) daily regimens, respectively. Regimen adherence was 13.1%, 24.9%, and 23.1% lower in twice- (n = 826), 3-times (n = 321), and 4-times (n = 86) daily regimens, respectively, compared with once-daily regimens (n = 2,118). Finally, compared with once-daily regimens (n = 936), timing adherence was 26.7%, 39.0%, and 54.2% lower for twice- (n = 650), 3-times (n = 343), and 4-times (n = 109) daily regimens, respectively.

Few study-level factors were found to have statistically significant effects on medication adherence in meta-regression analysis (Table 4). A statistically significant decrease in taking adherence was found in studies that blinded patients to electronic monitoring (–10.1%) or when follow-up was 168 days or longer (–8.7%). Blinding to electronic monitoring was also found to decrease regimen adherence to a statistically significant level (–12.4%), as was asthma as the target disease state (–21.0%) compared with cardiovascular disease (reference

TABLE 1 *Characteristics of Included Studies*

First Author, Year	Study Design	Disease State	Mean Age (Years)	Percent Male (%)	Drug Class	Blinded to EM?	Dosing Frequencies (n =)	Mean Duration of Follow-Up (Days)	Country
Clerisme-Beaty, 2011[10] (Standard education arms only)	O/R	Poorly controlled asthma	~35	25	Montelukast and placebo	NR	QD (n = 25) QD (n = 23)	28	United States
Doró, 2011[11]	O	HTN	61	45	Antihypertensives	NR	QD (n = 15) BID (n = 9) TID (n = 5)	89	Hungary
Favrat, 2011[12]	O/R	Vitamin deficiency	~69	46	Vitamin B12	NR	QD (n = 47)	28	Switzerland
Kronish, 2010[13]	O	CAD	59	53	Aspirin	No	QD (n = 105)	84	United States
Platt, 2010[14]	O	Anticoagulation	55	65	Warfarin	No	QD (n = 114)	141 (median)	United States
Stilley, 2010[15]	O/R	Hyperlipidemia	46	54	Lovastatin/placebo	No	QD (n = 157)	168	United States
Grosset, 2009[16]	O	Parkinson's disease	65	71	Antiparkinson agents	NR	QD (n = 57) BID (n = 44) TID (n = 113) QID (n = 57)	28 (median)	European countries
Udelson, 2009[17]	R	HF	~65	73	Beta-blockers	No	QD (n = 135) BID (n = 135) BID (n = 131)	140	United States
Yentzer, 2008[18]	O	Psoriasis	50	63	Acitretin	NR	QD (n = 22)	84	United States
Kardas, 2007[19]	R	Stable angina	57	41	Beta-blockers	No	QD (n = 47) BID (n = 49)	66	Poland
Rand, 2007[20]	O/R	Asthma	35	30	Montelukast/placebo	NR	QD (n = 346)	84	United States
Grosset, 2007[21] (Pre-intervention phase only)	O/R	Parkinson's disease	~61-65	38	Antiparkinson agents	NR	QD (n = 34) BID (n = 15) TID (n = 68) QID (n = 28)	84	United Kingdom
Márquez-Contreras, 2006[22] (Standard education arm only)	O/R	HTN	59	50	Antihypertensives	NR	QD (n = 100)	184	Spain
Charpentier, 2005[23]	R	T2DM	56	61	Sulfonylureas	NR	QD (n = 100) BID (n = 33) TID (n = 68)	187	France
Kardas, 2005[24]	R	T2DM	~61	46	Sulfonylureas	No	QD (n = 49) BID (n = 48)	121-123	Poland
Tu, 2005[25]	O/R	HF	62	31	Metoprolol	NR	BID (n = 80)	180-360	United States
Buelow, 2004[26]	O	Epilepsy	38	36	Antiepileptics	NR	BID (n = 15) TID (n = 4) QID (n = 2)	28[a]	United States
Clowes, 2004[27] ("No monitoring" arm only)	O/R	Osteopenia	62	0	Raloxifene	Yes	QD (n = 24)	336	United Kingdom
Girvin, 2004[30]	O/R	HTN	NR	NR	Antihypertensives	No	QD (n = 23)	84	United Kingdom
Kardas, 2004[28]	R	Stable angina	64	41	Isosorbide mononitrate	No	QD (n = 50) BID (n = 50)	62-64	Poland
de Klerk, 2003[29]	O	RA, PMR, gout	~63	43	RA, PMR, and gout drugs	No	QD (n = 17) QD (n = 12) QD (n = 17) BID (n = 20) BID (n = 25) TID (n = 13)	210	Netherlands
Hamilton, 2003[31]	O/R	HTN	58	51	Potassium/placebo	No	TID (n = 106) TID (n = 106)	28	United States
Laporte, 2003[32] (Standard education arms only)	O/R	Anticoagulation	67	41	Vitamin K antagonists	Yes	QD (n = 42)	83 (median)	France
Bohachick, 2002[6]	O	HF	56	70	ACE inhibitors	No	QD (n = 69) BID (n = 74) TID (n = 26)	84	United States
Winkler, 2002[33]	O	T2DM	69	68	Sulfonylureas	Yes	QD (n = 11) BID (n = 7)	54	Switzerland
Chung, 2000[34]	O	Asthma	29	56	Zafirlukast	Yes	BID (n = 47)	84	United Kingdom
Schwed, 1999[36]	O	Primary type II hyperlipidemia	57	100	Fluvastatin	No	QD (n = 39)	28	Switzerland

TABLE 1 Characteristics of Included Studies *(continued)*

First Author, Year	Study Design	Disease State	Mean Age (Years)	Percent Male (%)	Drug Class	Blinded to EM?	Dosing Frequencies (n=)	Mean Duration of Follow-Up (Days)	Country
Waeber, 1999a[37]	O/R	HTN	61	60	Aspirin/placebo	No	QD (n=501)	365	European countries
Waeber, 1999b[38]	O	HTN	79	63	Antihypertensives	No	QD (n=35)	84	Switzerland
Girvin, 1998[35]	R	HTN	62	64	Enalapril	NR	QD (n=25)[b] BID (n=25)[b]	112	United Kingdom
Mulleners, 1998[39]	O	Migraine	NR	26	Beta-blockers, pizotifen, or methysergide	Yes	QD (n=11) BID (n=11) TID (n=7)	54	United Kingdom
Rivers, 1998[40]	O	Epilepsy	34	67	Antiepileptics	No	BID (n=5)	84	United Kingdom
Leenen, 1997[41]	R	HTN	55	62	CCBs	No	QD (n=103) BID (n=82)	140	Canada
Paes, 1997[42]	O	T2DM	~69	40	Oral antidiabetic drugs	Yes	QD (n=40) BID (n=36) TID (n=15)	155	Netherlands
Vrijens, 1997[43]	O/R	HTN	NR	NR	Enalapril	NR	QD (n=127)	42	Belgium
de Klerk, 1996[44]	O/R	Ankylosing spondylitis	NR	NR	NSAIDs	No	QD (n=65)	225	Netherlands
Mallion, 1996[45]	O	HTN	58	58	Trandolapril	No	QD (n=501)	32	France
Mason, 1996a[46]	O	T2DM	68	100	Sulfonylureas	NR	QD (n=40) BID (n=30)	NR	United States
Mason, 1996b[47]	O	Anticoagulation	65	NR	Warfarin	Yes	QD (n=20)	60	United States
Straka, 1996[48]	O	Ischemic heart disease	67	37	Isosorbide dinitrate	No	TID (n=68)[c]	28	United States
Cramer, 1995[49]	O	Epilepsy	NR	NR	Antiepileptics	NR	BID (n=66) BID (n=66) TID (n=36) QID (n=23)	189	Canada
Brun, 1994[50]	R	Stable angina	~64	65	Isosorbide mononitrate	No	QD (n=16) BID (n=15)	78-79	Sweden
Kruse, 1994[51]	O	HTN	62	54	Antihypertensives	No	QD (n=15) BID (n=9)	214	Germany
Steiner, 1994[52]	O	Migraine	45	22	Pizotifen	Yes	TID (n=4)	56	United Kingdom
Kruse, 1993[53]	O/R	Familial hyper-cholesterolemia	~47	71	Lovastatin and placebo	No	QD (n=12)[b] QD (n=12)[b] QD (n=12)[b] QD (n=12)[b]	28	Germany
Rudd, 1993[54]	O	Chronic cardiovascular conditions	54	68	Cardiovascular medications	NR	QD (n=20) BID (n=8) TID (n=2)	84	United States
Rudd, 1992[55]	O/R	HTN	57	67	CCB or ACE inhibitor	No	BID (n=18)	147	United States
Eisen, 1990[56]	O/R	HTN	61 (median)	100	Antihypertensives	No	QD (n=45) BID (n=40) TID (n=20)	140	United States
Kruse, 1990[57]	O	Various chronic diseases	50	58	Antiepileptics, cardiac glycosides, lipid-lowering drugs, antidiabetic agents, diuretics, beta-blocker, aspirin, or theophylline	Mixed[d]	QD (n=12) BID (n=5) BID (n=4) TID (n=4) TID (n=4)	42	Germany
Cramer, 1989[58]	O	Epilepsy	NR	50	Antiepileptics	No	QD (n=3) BID (n=12) TID (n=7) QID (n=4)	132	United States
Eisen, 1987[59]	O	HTN	61 (median)	100	Thiazide diuretics	No	QD (n=24)	103	United States

[a]*Twenty-eight-day follow-up requested of study participants.*
[b]*Crossover study.*
[c]*TID regimen with a 10-hour nitrate-free period.*
[d]*Twenty-one patients were blinded to MEMS; 10 patients were not.*

ACE inhibitors = angiotensin-converting enzyme inhibitors; BID = twice daily; CAD = coronary artery disease; CCB = calcium channel blocker; EM = electronic monitoring; HF = heart failure; HTN = hypertension; MEMS = Medication Event Monitoring System; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; O = observational; O/R = observational analysis of data obtained from a randomized controlled trial; PMR = polymyalgia rheumatica; QD = once daily; QID = 4 times daily; R = randomized; RA = rheumatoid arthritis; T2DM = type 2 diabetes mellitus; TID = 3 times daily.

TABLE 2 *Taking, Regimen, and Timing Adherence Data for Included Studies*

Study, Year	Taking Adherence Mean (±SE) Percentage				Regimen Adherence Mean (±SE) Percentage				Timing Adherence Mean (±SE) Percentage			
	QD	BID	TID	QID	QD	BID	TID	QID	QD	BID	TID	QID
Clerisme-Beaty, 2011[10]	—	—	—	—	47.8±2.3 52.0±2.2	—	—	—	—	—	—	—
Doró, 2011[11]	98.4±0.8	92.9±2.8	88.4±6.0	—	—	—	—	—	91.1±2.4	60.4±11.7	54.3±10.0	—
Favrat, 2011[12]	98.6±1.6	—	—	—	93.1±1.9	—	—	—	89.8±2.6	—	—	—
Kronish,2010[13]	—	—	—	—	87.0±1.6	—	—	—	—	—	—	—
Platt, 2010[14]	—	—	—	—	78.8±1.8	—	—	—	—	—	—	—
Stilley, 2010[15]	81.1±2.1	—	—	—	70.7±2.0	—	—	—	—	—	—	—
Grosset, 2009[16]	101.3±2.0	97.3±2.4	92.1±1.7	84.4±3.0	92.0±2.0	75.4±3.9	77.4±2.4	56.4±4.3	87.1±2.8	29.1±7.3	26.2±1.7	12.0±2.0
Udelson, 2009[17]	88.2±2.1	89.3±1.8 87.1±2.2	—	—	—	—	—	—	—	—	—	—
Yentzer, 2008[18]	—	—	—	—	78.8±3.4	—	—	—	—	—	—	—
Kardas, 2007[19]	86.5±3.1	76.1±3.8	—	—	84.4±3.2	64.0±4.5	—	—	58.6±4.7	42.0±4.0	—	—
Rand, 2007[20]	—	—	—	—	77.5±1.2	—	—	—	—	—	—	—
Grosset, 2007[21]	—	—	—	—	—	—	—	—	76.4±3.8	28.5±7.2	22.2±2.4	13.7±1.3
Márquez-Contreras, 2006[22]	87.7±2.4	—	—	—	83.7±2.3	—	—	—	79.9±2.8	—	—	—
Charpentier, 2005[23]	87.0±1.6	84.0±2.6	79.0±2.1	—	87.0±1.6	—	—	—	—	—	—	—
Kardas, 2005[24]	93.5±2.0	87.2±3.0	—	—	86.3±2.2	66.9±4.2	—	—	62.0±3.2	43.2±3.8	—	—
Tu, 2005[25]	—	63.0±3.8	—	—	—	—	—	—	—	32.7±3.5	—	—
Beulow, 2004[26]	—	—	—	—	—	58.3±10.2	31.8±19.0	91.5±6.9	—	—	—	—
Clowes, 2004[27]	74.0±8.0	—	—	—	—	—	—	—	—	—	—	—
Girvin, 2004[30]	96.8±1.3	—	—	—	—	—	—	—	79.6±2.1	—	—	—
Kardas, 2004[28]	88.9±2.3	73.8±3.6	—	—	85.5±2.3	59.5±4.7	—	—	59.1±3.9	49.4±4.0	—	—
de Klerk, 2003[29]	96.0±3.3 65.0±8.4 84.0±4.1	82.0±3.8 72.0±6.1	77.0±8.2	—	88.0±2.3 44.0±9.2 74.0±5.6	68.0±5.9 55.0±5.9	67.0±10.2	—	—	—	—	—
Hamilton, 2003[31]	—	—	63.0±2.6	—	—	—	—	—	—	—	58.4±2.6	—
Laporte, 2003[32]	—	—	—	—	80.7±3.0	—	—	—	—	—	—	—
Bohachick, 2002[6]	97.6±1.5	93.1±1.5	88.9±2.7	—	90.1±2.0	83.8±2.8	68.4±5.8	—	87.9±2.3	69.7±3.5	52.6±5.3	—
Winkler, 2002[33]	101.0±1.4	82.9±10.7	—	—	93.6±1.7	63.4±12.1	—	—	—	—	—	—
Chung, 2000[34]	—	80.0±3.5	—	—	—	—	—	—	—	64.0±3.8	—	—
Schwed, 1999[36]	94.3±1.5	—	—	—	88.1±2.4	—	—	—	88.2±2.1	—	—	—
Waeber, 1999a[37]	—	—	—	—	78.2±1.1	—	—	—	—	—	—	—
Waeber, 1999b[38]	—	—	—	—	80.8±3.5	—	—	—	—	—	—	—
Girvin, 1998[35]	101.2±1.2	90.1±2.4	—	—	92.2±1.6	72.6±3.7	—	—	76.2±2.7	29.6±3.4	—	—
Mulleners, 1998[39]	—	—	—	—	79.8±5.2	60.0±9.0	54.2±10.6	—	—	—	—	—
Rivers, 1998[40]	—	—	—	—	—	88.6±5.5	—	—	—	—	—	—
Leenen, 1997[41]	94.0±1.0	91.0±2.0	—	—	90.0±2.0	82.0±2.0	—	—	86.0±2.0	76.0±2.0	—	—
Paes, 1997[42]	98.7±3.0	83.1±4.3	65.8±8.5	—	79.1±3.0	65.6±4.5	38.1±8.6	—	77.7±3.4	40.7±4.9	5.3±1.5	—
Vrijens, 1997[43]	94.3±1.0	—	—	—	—	—	—	—	—	—	—	—
de Klerk, 1996[44]	—	—	—	—	78.0±3.1	—	—	—	—	—	—	—
Mallion, 1996[45]	90.8±0.9	—	—	—	—	—	—	—	—	—	—	—
Mason, 1996a[46]	—	—	—	—	89.6±2.1	81.3±4.3	—	—	—	—	—	—
Mason, 1996b[47]	—	—	—	—	86.0±3.8	—	—	—	—	—	—	—
Straka 1996[48]	—	—	—	—	—	—	66.0±3.5	—	—	—	—	—
Cramer, 1995[49]	—	—	—	—	—	89.0±0.9 86.0±1.4	80.0±3.0	80.0±4.8	—	66.0±3.0 59.0±3.2	40.0±3.2	33.0±3.8
Brun, 1994[50]	99.0±0.9	95.0±3.1	—	—	98.0±0.8	87.8±6.1	—	—	58.0±14.7	48.8±9.6	—	—
Kruse, 1994[51]	88.8±4.6	87.9±6.9	—	—	84.8±5.9	79.8±8.2	—	—	—	—	—	—
Steiner, 1994[52]	—	—	—	—	—	—	58.4±14.5	—	—	—	32.8±6.7	—
Kruse, 1993[53]	92.0±4.5 90.4±5.4 95.3±2.0 88.7±3.3	—	—	—	—	—	—	—	67.3±8.4 60.9±9.6 66.8±7.6 62.2±7.3	—	—	—
Rudd, 1993[54]	81.8±5.3	75.9±12.7	72.4±19.8	—	—	—	—	—	—	—	—	—
Rudd, 1992[55]	—	84.4±4.2	—	—	—	60.5±4.7	—	—	—	46.3±4.3	—	—
Eisen, 1990[56]	96.0±1.0	93.0±1.9	83.8±3.4	—	83.6±3.0	74.9±3.2	59.0±6.8	—	—	—	—	—
Kruse, 1990[57]	77.1±6.4	—	—	—	76.5±4.6	61.4±12.4 85.0±5.3	54.0±7.3 46.6±5.4	—	—	—	—	—
Cramer, 1989[58]	—	—	—	—	87.0±6.4	81.0±4.9	77.0±4.5	39.0±12.0	—	—	—	—
Eisen, 1987[59]	97.0±1.6	—	—	—	—	—	—	—	84.0±3.1	—	—	—

BID = twice daily; QD = once daily; QID = 4 times daily; SE = standard error; TID = 3 times daily; — = data not available.

TABLE 3 *Traditional Meta-Analysis of Dosing Frequency Analyses of Taking, Regimen, and Timing Adherence*[a]

Frequency of Dosing	N (%) Groups [N of Patients] in Taking Adherence Analysis	Taking Adherence[b] (95% CI)	N (%) Groups [N of Patients] in Regimen Adherence Analysis	Regimen Adherence[c] (95% CI)	N (%) Groups [N of Patients] in Timing Adherence Analysis	Timing Adherence[d] (95% CI)
Once daily	33 (50.8) [n = 2,006]	93.0 (91.2-94.7)	35 (46.1) [n = 2,118]	81.8 (77.9-85.7)	20 (42.6) [n = 936]	76.9 (72.5-81.3)
Twice daily	22 (33.8) [n = 1,259]	85.6 (82.5-88.8)	24 (31.6) [n = 826]	74.2 (70.0-78.5)	16 (34.0) [n = 650]	59.3 (40.6-58.0)
Three times daily	9 (13.8) [n = 362]	80.1 (72.0-88.2)	13 (17.1) [n = 321]	62.8 (55.4-70.1)	8 (17.0) [n = 343]	35.9 (21.8-50.1)
Four times daily	1 (1.5) [n = 57]	84.4 (78.5-90.3)	4 (5.3) [n = 86]	68.2 (48.9-87.4)	3 (6.4) [n = 109]	18.8 (10.1-27.5)

[a]*Weighted by the inverse of the variance of medication adherence.*
[b]*Taking adherence was defined as the number of openings divided by the prescribed number of doses.*
[c]*Regimen adherence was defined as the percentage of days with the appropriate number of doses taken.*
[d]*Timing adherence was defined as the percentage of near optimal interadministration intervals.*
CI = confidence interval.

TABLE 4 *Results of Meta-Regression Analyses of Taking, Regimen, and Timing Adherence*[a]

Study-Level Factor	Adjusted Difference in Taking Adherence[b] (95% CI)	Adjusted Difference in Regimen Adherence[c] (95% CI)	Adjusted Difference in Timing Adherence[d] (95% CI)
Frequency of dosing			
Once daily	Referent	Referent	Referent
Twice daily	–6.7 (–11.0 to –2.4)	–13.1 (–19.6 to –6.6)	–26.7 (–35.8 to –17.8)
Three times daily	–13.5 (–19.4 to –7.6)	–24.9 (–33.1 to –16.7)	–39.0 (–51.2 to –26.8)
Four times daily	–19.2 (–36.3 to –2.1)	–23.1 (–37.0 to –9.2)	–54.2 (–71.8 to –36.6)
Year of publication			
After 2000	–0.8 (–5.1 to 3.5)	–4.6 (–10.3 to 1.1)	–0.7 (–9.3 to 7.9)
2000 or prior	Referent	Referent	Referent
Country			
United States	–3.2 (–8.1 to 1.7)	–4.5 (–12.3 to 3.3)	6.5 (–4.9 to 17.9)
Not United States	Referent	Referent	Referent
Study design			
Randomized	–2.8 (–8.1 to 2.5)	–3.1 (–13.3 to 7.1)	–13.1 (–24.4 to –1.3)
O/R	–2.5 (–7.4 to 2.4)	–4.2 (–13.2 to 4.8)	–14.7 (–24.1 to –5.3)
Observational	Referent	Referent	Referent
Blinded to EM			
Yes	–10.1 (–18.7 to –1.5)	–12.4 (–21.8 to –3.0)	–11.7 (–33.1 to 9.7)
No/Indeterminate	Referent	Referent	Referent
Disease state			
Cardiovascular	Referent	Referent	Referent
Neurologic	7.7 (–2.3 to 17.7)	1.5 (–7.3 to 10.3)	–7.4 (–19.2 to 4.4)
Type 2 diabetes	4.5 (–3.3 to 12.3)	0.0 (–9.4 to 9.4)	–8.2 (–25.1 to 8.7)
Asthma	–0.1 (–17.0 to 17.2)	–21.0 (–36.4 to –5.1)	17.5 (–14.3 to 49.3)
Other/mixed	–2.9 (–10.5 to 4.7)	–7.6 (–16.8 to 1.6)	20.2 (–6.1 to 46.5)
Follow-up at least 168 days			
Yes	–8.7 (–14.4 to –3.0)	–2.6 (–10.8 to 5.6)	4.6 (–7.9 to 17.1)
No	Referent	Referent	Referent

[a]*Results from a multiple-linear, mixed-method model controlling for the study-level factors shown in the table.*
[b]*Taking adherence was defined as the number of openings divided by the prescribed number of doses.*
[c]*Regimen adherence was defined as the percentage of days with the appropriate number of doses taken.*
[d]*Timing adherence was defined as the percentage of near optimal interadministration intervals.*
CI = confidence interval; EM = electronic monitoring; O/R = observational analysis of data obtained from a randomized controlled trial.

group). Neither randomization by dosing frequency nor *post hoc* observational analysis of randomized trial data were significant predictors of taking or regimen adherence compared with observational analysis (reference group); however, randomized design was associated with reduced timing adherence.

Discussion

This meta-analysis found that patients with chronic diseases are most adherent to medication regimens that require them to take drugs once daily compared with more frequent dosing regimens based on electronic measurement of adherence.

Specifically, twice-daily, 3-times daily, and 4-times daily dosing regimens had progressively lower weighted mean adherence rates compared with once-daily regimens, a finding that was robust to multiple adherence definitions. While timing adherence may not be clinically important for every drug, the consistent finding that more frequent dosing was associated with decreased adherence across all the definitions lends credence to our results.

However, even the use of once-daily regimens did not guarantee perfect adherence (76.9% to 93.0%); therefore, one can conclude that frequency is not the only modifier of adherence. Other factors that were independently negatively associated with medication-taking adherence included blinding to electronic monitoring and longer follow-up periods. In addition, regimen adherence was statistically significantly lower when the chronic disease studied was asthma compared with cardiovascular disease. Typically, adherence rates increase when patients know they are being watched, and as expected, patients blinded to electronic monitoring demonstrated decreased adherence in this analysis. The finding that longer follow-up periods led to decreased adherence was expected, as adherence rates in chronic conditions typically drop off most significantly after 6 months.[5] The reduced adherence rate in studies of asthma is difficult to explain as there were only 3 studies, and all 3 included only second-line therapies. One may speculate that patients may have been nonadherent due to lack of efficacy or that the disease state itself has an impact on adherence; however, more data are needed to draw an accurate conclusion. Timing adherence was also decreased when researchers used a randomized trial design.

Claxton et al., who produced the most recent meta-analysis of the effect of dosing frequency on adherence, used methods to statistically pool data from included trials to evaluate taking adherence across multiple dose frequencies.[3] They found that taking adherence was significantly higher with once-daily compared with 3-times or 4-times daily regimens (79%, 65%, and 51%, respectively; $P<0.001$) and with twice-daily compared with 4-times daily regimens (69% vs. 51%; $P=0.001$). However, the researchers found no significant differences between the once-daily and twice-daily or twice-daily and 3-times daily treatment regimens after Bonferroni adjustment of *P* values.

A lack of data may have prohibited Claxton et al. from achieving enough statistical power to detect a true difference. This problem was a primary reason for conducting the present study, as an additional 26 studies published after the study by Claxton et al. were included. Also of concern was the method by which Claxton et al. performed their statistical analysis. According to the Cochrane Handbook for Systematic Reviews, when conducting a meta-analysis, studies should be weighted based upon the inverses of their variances; in other words, studies with more precise estimates have a larger impact on the final results.[60] Claxton et al. instead calculated simple averages of the mean adherence rates of all the included studies. This approach may have been reasonable at the time but is an imperfect technique by today's standards.

Similar to the current analysis, Claxton et al. included a heterogeneous patient population. However, Claxton et al. included both acute and chronic diseases along with various dosage forms (e.g., oral, inhaled, topical, and ophthalmic) in the analysis. Such heterogeneous disease states and dosage forms likely had a major confounding effect on their results. Without correction for this heterogeneity, application of the results remains challenging. The present study addressed these issues by excluding studies of nonoral dosage forms and acute disease states as well as attempting to correct for confounding through statistical techniques. Both traditional random-effects meta-analysis (which assumes that studies are estimating different but related effects and therefore makes an adjustment to the studies' weighting based upon the extent of variation or heterogeneity between them [often measured by the Cochrane Q or I2 statistic]) and multivariate mixed-linear model meta-regression analysis were conducted.[60] Meta-regression was used to adjust for the potential confounding effect of other study-level characteristics.

It is estimated that almost 90% of Americans aged 60 years or older take at least 1 prescription medication, typically on a scheduled basis.[61] Despite evidence for an association between medication adherence and improved quality of life, medication adherence rates for patients with chronic conditions are estimated at only 50%-60%.[62-67] The effectiveness of prescription drugs for chronic diseases is likely diminished when patient adherence is suboptimal; thus, it is not surprising that poor medication adherence has been associated with higher morbidity, mortality, and health care costs.[68-74] Of note, it is thought that 33%-69% of medication-related hospital admissions in the United States are the result of poor medication adherence, with a total estimated price tag of more than $100 billion per year.[68,69,75,76] Consequently, it would seem prudent to take reasonable steps to improve patient medication adherence, such as the selection of drugs with less frequent daily dosing, while at the same time remembering to consider whether any additional costs will be outweighed by the benefits.

Limitations

There are some limitations to the meta-analysis that should be noted. First, much of the published medication adherence literature involves studies of small sample sizes and in populations with differing disease states. In an attempt to overcome these obstacles, we conducted a multivariate meta-regression analysis to adjust for multiple study-level characteristics.[4] However, it is unlikely we were able to adjust for all important sources of heterogeneity between studies, and we cannot rule out the presence of residual confounding. These realities have made it more difficult to draw firm conclusions regarding the

association between dosing frequency and medication adherence.

Second, monitoring adherence via electronic devices may not be considered a "real-world" process; however, these devices do provide the most detailed data on adherence. Patient self-reports often suffer from erroneous accounts of taken or missed doses, while blood-level monitoring may indicate only whether a patient took the most recent doses. Prescription refills also provide questionable adherence information because they do not indicate the timing of intake, whereas electronic monitoring devices are able to provide those data.[3]

A third limitation is the small sample sizes of the 4-times daily groups. It is unlikely that there will be a time when a physician must choose between once-daily and 4-times daily medications; however, including 4-times daily groups in the analysis at the very least verifies the notion that there is an inverse relationship between dosing frequency and medication adherence. Fourth, there is also concern that the exclusion of studies with suboptimal reporting could have affected the present study results. Through the literature search, a number of studies were identified that could have provided useful data for this analysis but had to be excluded due to their failure to report a measure of statistical variance (a standard deviation, standard error, or confidence interval). Despite great effort in contacting the corresponding authors to obtain the information that would have allowed us to include these studies, not all authors responded to the requests.

Conclusion

Although the heterogeneous population precludes the ability to draw firm conclusions regarding specific diseases and adherence rates, this analysis demonstrated an inverse relationship between medication adherence and dosing frequency in patients with chronic disease.

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APPENDIX Search Strategy for MEDLINE and Embase

#1 'patient compliance'/exp OR 'patient compliance' OR 'medication adherence'/exp OR 'medication adherence' OR adhere* OR comply OR complian* OR non?adhere* OR non?complian*

#2 medication* AND event AND monitor* AND systems* OR 'mems'/exp OR mems OR electronic AND monitor* OR adhere* AND monitor* OR 'microprocessor'/exp OR microprocessor

#3 'pill'/exp OR pill AND box* OR 'pill'/exp OR pill AND container* OR 'medication'/exp OR medication AND vial OR 'pill'/exp OR pill AND vial OR pillbox*

#4 electronic OR electronically

#5 #2 OR #3

#6 #4 AND #5

#7 #1 AND #6

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