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ORIGINAL RESEARCH

Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis

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Objectives: To assess the impact of reduced frequency of oral therapies from multiple-dosing schedules to a once-daily (OD) dosing schedule on adherence, compliance, persistence, and associated economic impact.

Methods: A meta-analysis was performed based on relevant articles identified from a comprehensive literature review using MEDLINE® and Embase®. The review included studies assessing adherence with OD, twice-daily (BID), thrice-daily (TID), and four-times daily (QID) dosing schedules and costs associated with optimal/suboptimal adherence among patients with acute and chronic diseases. Effect estimates across studies were pooled and analyzed using the DerSimonian and Laird random-effect model.

Results: Forty-three studies met inclusion criteria, and meta-analyzable data were available from 13 studies. The overall results indicated that OD schedules were associated with higher adherence rates (odds ratio [OR] 3.07, 95% confidence interval [CI] 1.80–5.23; $P < 0.001$ for OD versus > OD dosing) and compliance rates (OR 3.50, 95% CI 1.73–7.08; $P < 0.001$ for OD versus > OD dosing); persistence rates showed the same direction but were not statistically significant (OR 1.43, 95% CI 0.62–3.29; $P = 0.405$ for OD versus BID dosing). Results for each of the conditions were consistent with those observed overall with respect to showing the benefits of less frequent dosing. From a health economic perspective, higher adherence rates with OD relative to multiple dosing in a number of conditions were consistently associated with corresponding lower costs of health care resources utilization.

Conclusion: Current meta-analyses suggested that across acute and chronic disease states, reducing dosage frequency from multiple dosing to OD dosing may improve adherence to therapies among patients. Improving adherence may result in subsequent decreases in health care costs.

Keywords: compliance, dosage frequency, persistence, random-effect meta-analyses

Introduction

Worldwide public health efforts to address a variety of chronic conditions are being undermined by an alarmingly low adherence to therapies.[1] Nonadherence is a serious problem in patients on long-term treatment, accounting for up to 50% of cases where drugs fall short of their therapeutic goals.[2–4] For nonadherent patients, the benefits of extended duration of treatment may not be sufficiently apparent.[2,3] Adherence problems are prevalent where self-administration of treatment is required, including acute and chronic illnesses such as hypertension,[5] depression,[6] diabetes,[7] HIV/AIDS,[8] transplant,[9] and cardiovascular (CV) disorders.[10]

Nonadherence to treatment is a difficult issue to evaluate due to inconsistent definitions and measurement methodologies.[11] Standard definitions of adherence,

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compliance, and persistence were developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group.[12] According to the group, medication compliance (synonym: adherence) refers to conforming to the recommendations made by a provider with respect to timing, dosing, and frequency of medication taking.[12] Medication persistence refers to conforming to a recommendation of continuing treatment for the prescribed length of time.[12] A wide variety of factors contribute to nonadherence,[13,14] including drug regimen complexity as a major contributing factor.[15]

Until 2006, published reviews and meta-analyses focusing on adherence, compliance, and persistence demonstrated that decreasing the number of doses taken daily provides benefits in terms of medication-taking behaviour.[15–19] These reviews and meta-analyses neither examined observational studies nor assessed the impact on associated costs.

To fill this gap, a comprehensive literature review and meta-analyses were conducted to assess the impact of multiple-daily dosing and once-daily (OD) dosing of oral therapies prescribed in acute and chronic diseases on adherence, compliance, persistence, and health care costs. The authors of the current study would also like to note that subsequent to our analyses and prior to submission for publication, a comprehensive and rigorous meta-analytic study was published that evaluated the relationship between dosing frequency and medication adherence in studies of patients with chronic diseases.[20] That study, which provides a valuable update of the literature, confirmed the inverse relationship between medication adherence and dosing frequency, with once daily dosing shown to be associated with the greatest adherence. However, similar to other studies, there was no evaluation of the impact of dosing frequency on costs, and neither did that study stratify the analyses by disease states.

Materials and methods

The original objective was to compare adherence to OD dosing regimen with that of multiple-dosing regimens in patients with chronic pain but, because of the lack of published evidence in this disease area, the investigation was expanded by not including a term that would have limited the search to chronic pain. This comprehensive literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[21]

Study eligibility criteria

This review included comparative studies published in English and assessed adherence/compliance/persistence with OD, twice-daily (BID), three-times daily (TID), or four-times daily (QID) dosing, including associated costs among patients with acute and chronic diseases. There was no restriction on the treatments assessed in the study other than that they were orally administered.

Data source and evidence synthesis

The search was conducted in MEDLINE® (including MEDLINE® In-Process) and Embase® up to September 16, 2011. All retrieved studies were screened, and only those meeting predefined eligibility criteria (Appendix) were included in the review.

Initial screening of the retrieved citations was conducted independently by two reviewers on the basis of the title and the abstract. Any discrepancy between the reviewers was reconciled by a third reviewer. The full-text publications of all citations of potential interest were then screened for inclusion by two independent reviewers, with all disagreements reconciled by a third reviewer. Relevant data from all included studies were extracted independently by two reviewers using a predefined extraction grid; any differences were then resolved by a third independent reviewer.

Extracted data included percentage of patients adherent and nonadherent to therapy, medication possession ratio (MPR), and odds ratio (OR) or risk ratio or β-coefficient to evaluate the association between adherence with different dosing schedules. Costs associated with optimal/suboptimal adherence and quality-adjusted life-years (QALYs) were also extracted. The same type of extraction for adherence was performed for compliance and persistence. Due to variability in definitions of adherence/compliance/persistence across studies, no single definition criteria was used to define these parameters. The studies were classified as evaluating adherence/compliance/persistence based on author definitions in the associated studies for the purpose of quantitative analyses.

Statistical analysis

Random-effect meta-analyses using the DerSimonian and Laird random-effects model were conducted.[22] Estimated ORs for the studies were combined using Stata® v11.1. For the purpose of analysis, data for all dosing schedules administered more than OD were pooled under > OD regimen group; $P \leq 0.05$ was considered statistically significant.

The statistical heterogeneity within each analysis was assessed using the I^2 statistic.[23] Multivariate-adjusted effect estimates were included in the meta-analysis; however, when multivariate effect estimates were not available, unadjusted ORs were computed from the treatment distributions for those with and without the event of interest reported in the published articles. A linear meta-regression considering random-effect modeling was performed using Stata® v11.1 (Stata Statistical Software: Release 12. StataCorp LP, College Station, TX, USA) to explore the effect on adherence, compliance, or persistence with respect to different dosing schedules.[24]

Results

The search terms and strategy are shown in Table 1, and the schematic selection process of studies from the identified records is presented in Figure 1. Forty-three studies (44 publications) fulfilled the inclusion criteria and provided the basis for this review, encompassing a variety of acute and chronic conditions in addition to pain. The characteristics of these studies including the outcome evaluated (eg, adherence, compliance, and/or persistence) are summarized in Table 2. Of these 43 studies, 13 were amenable to conducting random-effect meta-analyses. Studies with non-meta-analyzable data were discussed descriptively.

Overall associations

Overall association of adherence with dosing frequencies

Random-effects meta-analysis was conducted on pooled ORs derived from various disease conditions to compare OD versus BID, BID versus TID, and OD versus > OD regimens in terms of adherence. OD dosing was associated with significantly better adherence rates compared with BID (seven studies, OR 2.20, 95% confidence interval [CI] 1.09–4.41, $P = 0.027$, $I^2 = 95.5\%$). No significant difference was observed between BID and TID dosing (three studies, OR 1.88, 95% CI 0.85–4.13, $P = 0.118$, $I^2 = 61.9\%$). OD dosing showed significantly greater adherence rates compared with > OD dosing (ten studies, OR 3.07, 95% CI 1.80–5.23, $P < 0.001$, $I^2 = 91.3\%$) (Figure 2).

A random-effects model regression plot using 13 point estimates (ten studies) for adherence using OD dosing as reference showed that an increase by one dose daily (eg, OD to BID) resulted in a twofold reduction in the odds of adherence (OR 2.03, 95% CI 1.84–7.46).

Overall association of compliance with dosing frequencies

Random-effects meta-analysis of pooled ORs across disease conditions demonstrated OD dosing had significantly better compliance than >OD dosing (six studies, OR 3.50, 95% CI 1.73–7.08, $P < 0.001$, $I^2 = 69.0\%$) (Figure 3). A similar trend was observed for OD versus BID dosing (six studies, OR 4.08, 95% CI 1.68–9.91, $P = 0.002$, $I^2 = 73.4\%$).

Association of persistence with dosing frequencies

Pooling the data across disease conditions, random-effects meta-analyses illustrated high persistence rates with OD compared with BID dosing (three studies, OR 1.43, 95% CI 0.62–3.29, $P = 0.405$, $I^2 = 96.9\%$) (Figure 4). However, due to considerable heterogeneity between studies, the results should be interpreted with caution.

Sensitivity analysis

Sensitivity analyses conducted by study design indicated no differential effects compared with that of the results indicated by the overall meta-analysis. A higher magnitude of effect was observed with OD compared with the other dosing regimens. For prospective studies,[25–34] adherence of OD versus > OD resulted in an OR of 7.11 (95% CI 1.98–25.59, $P = 0.003$) and compliance of OD versus > OD had an OR of 3.61 (95% CI 1.68–7.78, $P = 0.001$). In the retrospective studies,[6,7,35–37] adherence of OD versus > OD showed an OR

Table 1 Search terms and initial strategy for identifying relevant studies

Search number	Search strings
1	(once OR twice OR thrice OR one OR two OR three) NEAR/1 (daily* OR per*day) OR 'OD':ab,ti OR 'BID':ab,ti OR 'TID':ab,ti OR 'QID':ab,ti
2	adhere*:ab,ti OR nonadhere*:ab,ti OR (non NEAR/1 adhere*):ab,ti OR complian*:ab,ti OR noncomplian*:ab,ti OR (non NEAR/1 complian*):ab,ti OR 'medication possession':ab,ti OR mpr:ab,ti OR 'persistence':ab,ti OR (non NEAR/1 persist*):ab,ti OR nonpersisten*:ab,ti OR 'medication possession ratio' OR 'treatment refusal' OR 'medication compliance'/exp OR medication NEAR/1 complian* OR medication NEAR/1 persisten* OR medication NEAR/1 adhere*
3	patient NEAR/1 (monitoring OR care OR counselling)
4	#2 OR #3
5	#1 AND #4

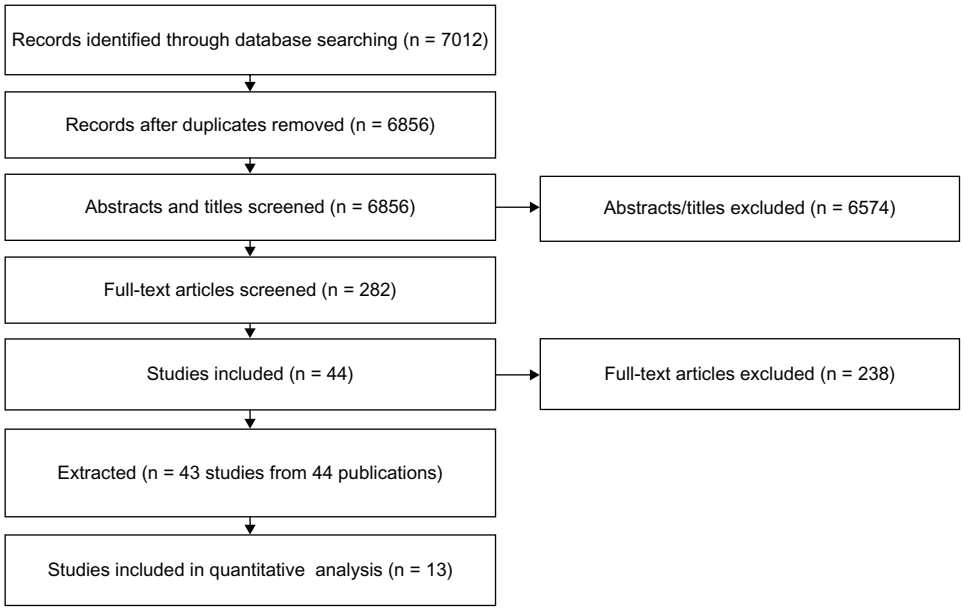

Figure 1 Search terms and strategy for identifying relevant studies.

of 2.37 (95% CI 1.98–2.83, $P < 0.001$), and persistence of OD versus BID resulted in an OR of 1.43 (95% CI 0.62–3.27, $P = 0.401$). Adherence of OD versus > OD in cross-sectional studies[37–39] resulted in an OR of 2.39 (95% CI 0.60–9.49, $P = 0.217$).[38–40]

Combining the pooled estimates (Z-statistic) between different study designs (cross-sectional, prospective, retrospective, randomized controlled trial [RCT], non-RCT) and analysis types (multivariate, univariate) to examine adherence/persistence/compliance rates for OD dosing versus > OD dosing across disease conditions did not show evidence of bias in results.

Publication bias

Funnel plots showed no marked asymmetry and Egger's tests demonstrated statistically nonsignificant differences; $P = 0.80$ for compliance of OD versus > OD in prospective studies and $P = 0.24$ for adherence of OD versus > OD in cross-sectional studies.[41,42] However, visual inspection of the funnel and Egger's plots indicated that publication bias or other biases cannot be completely ruled out, and such bias might have been introduced in the process of locating, selecting, and combining studies.

Disease-specific association of adherence with dosing frequencies

Cardiovascular disorders

Thirteen studies evaluated the association of adherence/persistence/compliance with different dosing schedules among CV disorders including hypertension,[29,30,34,40,43–45] angina pectoris,[46,47] atrial fibrillation,[10] heart transplant,[48] and acute coronary syndrome (Table 3).[37]

Random-effect meta-analysis for compliance indicated that OD dosing was associated with significantly higher compliance rates compared with BID dosing in three studies (OR 2.42, 95% CI 1.33–4.40, $P = 0.004$, $I^2 = 0\%$) (Table 3).[29,30,34] Patients with OD dosing were approximately 2.5 times as likely to comply with therapy than BID dosing of antihypertensive medications. Similarly, random-effect meta-analysis for persistence to medications for acute coronary syndrome showed no difference between OD and BID dosing (OR 0.85, 95% CI 0.65–1.11, $P = 0.235$, I^2 = not applicable).[37]

In contrast to the above results, Turki and Sulaiman[40] showed significantly greater adherence with multiple doses (BID and >BID) of antihypertensive medications compared with OD dosing ($P < 0.001$). All other empirical studies on CV disorders (atrial fibrillation, heart transplant, and angina) demonstrated an improvement in adherence, compliance, and persistence to OD dosing compared with BID dosing.[10,47–49]

Brown et al[46] developed a decision-analytic model to compare costs of treating exercise-induced angina with OD versus BID isosorbide mononitrate. Fewer medical resources were consumed by patients treated with OD versus BID dosing. The economic data suggested that, even though the per-tablet cost of OD was more than BID, the annual patient management costs were nearly the same for both regimens due to better compliance with the OD regimen (Table 4).[46]

Table 2 Summary of included studies for a dosage frequency comparison in medication treatments for chronic diseases

Disease sub-type	Study	Intervention	Number of patients	Mean duration (range) of follow-up in weeks	Study country(ies)	Outcome assessed
Hypertension	Celis[43]	Isradipine RF: BID	12	9.4	NR	Compliance
		Isradipine MR: OD	12			
	Baird[29]	Betaloc® Durules®: OD	193	NR	Canada and UK	Compliance
		Betaloc®: BID	196			
	Maro[34]	Antihypertensive: OD	61	156	Tanzania	Compliance*
		Antihypertensive: BID	34			
		Antihypertensive: TID	51			
	Turki[40]	Antihypertensive: OD	209	NR	Malaysia	Adherence*
		Antihypertensive: BID	148			
		Antihypertensive: ≥TID	23			
	Girvin[44]	Enalapril: OD	25	16	Ireland	Compliance
		Enalapril: BID	25			
	Andrejak[30]	Trandolapril: OD	71	26	France	Compliance*
		Captopril: BID	62			
	Boissel[45]	Nicardipine: TID	3636	12	France	Compliance
		Nicardipine SR: BID	3638			
Angina pectoris	Brown[46,†]	ISMN: OD	NR	NR	UK	Cost (total, direct, and indirect)
		ISMN: BID	NR			
	Kardas[47]	Betaxolol: OD	56	10	Poland	Compliance*
		Metoprolol tartrate: BID	56			
Cardiovascular disorders	Bae[49]	Cardiovascular regimen: BID	1,077,936	NR	NR	Adherence*
		Cardiovascular regimen: OD				
Atrial fibrillation	Song[10]	Carvedolol: OD	28,384	NR	NR	Persistence*
		Carvedolol: BID				
		Amlodipine: OD				
		Captopril: TID				
Acute coronary syndrome (ACS)	Hess[37]	Carvedilol at 6 months: OD	168	52	NR	Persistency, MPR, compliance
		Carvedilol at 6 months: BID	2086			
		Metformin at 6 months: OD	136			
		Metformin at 6 months: BID	614			
		Carvedilol at 12 months: OD	168			
		Carvedilol at 12 months: BID	2086			
		Metformin at 12 months: OD	136			
		Metformin at 12 months: BID	614			
Heart transplant	Doesch[48]	Tacrolimus/Cyclosporin A: BID	50	4	NR	Adherence*
		Tacrolimus: OD	50			
Depression	McLaughlin[36]	Bupropion: OD	756	NR	USA	Persistence*
		Bupropion: BID	2382			
	Granger[39]	Bupropion: OD	142	NR	NR	Adherence*
		Bupropion: BID	349			

(*Continued*)

Table 2 (*Continued*)

Disease sub-type	Study	Intervention	Number of patients	Mean duration (range) of follow-up in weeks	Study country(ies)	Outcome assessed
		Bupropion: TID	31			
	Stang[6]	Bupropion SR: BID	12,468	NR	USA	Persistence*, adherence, MPR
		Bupropion XL: OD	257,049			
	Stang[50]	Bupropion SR: BID	1917	39	USA	Persistence*, MPR
		Bupropion XL: OD	1074			
Schizophrenia	Pfeiffer[52]	Antipsychotic medication: OD	1381	NR	USA	Adherence*
		Antipsychotic medication: Multiple daily dosing	258			
Epilepsy	Cramer[51]	Antiepileptics: OD regimen	3	14	NR	Compliance*
		Antiepileptics: BID regimen	12			
		Antiepileptics: TID regimen	7			
		Antiepileptics: QID regimen	4			
Pain	Carlos[54,†]	Duloxetine: OD	NR	13	Mexico	Cost-effectiveness*
		Gabapentin: TID	NR			
		Pregabalin: BID	NR			
Migraine	Mulleners[53]	Propranolol: OD	11	NR	UK	Compliance
		Atenolol: BID	11			
		Pizotifen or methysergide: TID	7			
Type 2 Diabetes	Winkler[27]	Sulfonylureas OD: adherence by pill count > 90%	11	7.7	Germany	Adherence*
		Sulfonylureas OD: adherence by MEMS (dosage) > 90%	11			
		Sulfonylureas OD: adherence by MEMS (regimen) > 90%	11			
		Sulfonylureas OD: adherence by pill count 90%–110%	11			
		Sulfonylureas OD: adherence by MEMS (dosage) 90%–110%	11			
		Sulfonylureas OD: adherence by MEMS (regimen) 90%–110%	11			
		Sulfonylureas BID/TID: adherence by pill count > 90%	8			
		Sulfonylureas BID/TID: adherence by MEMS (dosage) > 90%	8			
		Sulfonylureas BID/TID: adherence by MEMS (regimen) > 90%	8			
		Sulfonylureas BID/TID: adherence by pill count 90%–110%	8			
		Sulfonylureas BID/TID: adherence by MEMS (dosage) 90%–110%	8			
		Sulfonylureas BID/TID: adherence by MEMS (regimen) 90% –110%	8			
	Dezii[7]	Glipizide GITS: OD	746	51.3	NR	Adherence index*, persistence*
		Glipizide: BID	246			
	Kardas[55]	Gliclazide MR: OD	55	16	Poland	Compliance*
		Glibenclamide: BID	50			
	Pullar[33]	Phenobarbital: BID	59	4	England	Compliance*, inadequate compliance, safety
		Phenobarbital: BID	60			
		Phenobarbital: TID	60			
	Charpentier[56]	Glimepiride: OD	100	26 (10-week dose titration and 16-week maintenance period)	France	Compliance*
		Glibenclamide: BID/TID	101			

HIV/AIDS	Carrieri[8]	HAART: OD	1110	260	France	Non-adherence*
		HAART: BID				
		HAART: ≥TID				
	Negredo[25]	HAART: OD	85	48	NR	Adherence
		HAART: BID	84			
	Stone[57]	ART: ≤2 doses daily (self-reported)	170	NR	USA	Adherence
		ART: ≥3 doses daily (self reported)	119			
		ART: ≤2 doses daily (correct)	141			
		ART: ≥3 doses daily (correct)	148			
	Abellan[58]	Ritonavir: BID	45	NR	Spain	Adherence*
		Indinavir: TID	70			
		Saquinavir: TID	49			
	Echarri	HAART: OD	75	26	Spain	Adherence*
	Martinez[35]	HAART: BID	217			
		HAART: TID	6			
	Moyle[38]	ART: OD	15	NR	France,	Adherence*
		ART: BID	255		Germany,	
		ART: TID	109		Italy, Spain,	
		ART: >TID	58		UK	
Respiratory tract infections (RTI)	Kardas[31]	Respiratory tract infection therapy: OD	250	0.9	Poland	Compliance*
		Respiratory tract infection therapy: BID	251			
	Kardas[32]	Clarithromycin: OD	60	1	Poland	Compliance*
		Clarithromycin: BID	62			
Community-acquired pneumonia/acute bronchitis	Spiritus[59,†]	Clarithromycin: BID	311	2	USA	Health care resource utilization*
		Erythromycin stearate: QID	321			
		Cefaclor: TID	302			
Streptococcal pharyngitis	Raz[60]	Penicillin V: BID	51	4	NR	Compliance
		Penicillin V: QID	53			
Renal transplantation	Abecassis[61,†]	Tacrolimus + mycophenolate mofetil: OD	NR	NR	USA	Economic outcomes (patient treatment cost)*
		Tacrolimus + mycophenolate mofetil: BID	NR			
	Sidhu[9,†]	Tacrolimus: OD	NR	NR	UK	Economic outcomes
		Tacrolimus: BID	NR			
Liver transplant	Eberlin[62]	Tacrolimus OD: post transplantation duration > 6 months to <2 years	16	52	NR	Compliance*
		Tacrolimus OD: post transplantation duration > 2 to <5 years	22			
		Tacrolimus OD: post transplantation duration > 5 years	21			
		Tacrolimus BID: post transplantation duration > 6 months to <2 years	15			
		Tacrolimus BID: post transplantation duration > 2 to <5 years	23			
		Tacrolimus BID: post transplantation duration > 5 years	22			
Ulcerative colitis	Hawthorne[28]	Asacol®: OD	103	52	UK	Adherence
		Asacol®: TID	110			
	Lachaine[63]	Mesalamine at 13 weeks: OD	12	52	Canada	Adherence*, persistence*, compliance

(*Continued*)

Table 2 (*Continued*)

Disease sub-type	Study	Intervention	Number of patients	Mean duration (range) of follow-up in weeks	Study country(ies)	Outcome assessed
		Mesalamine at 13 weeks: >OD	10			
		Mesalamine at 26 weeks: OD	12			
		Mesalamine at 26 weeks: >OD	10			
	Kane[26]	Mesalamine: OD	12	26	USA	Adherence, medication consumption rates
		Mesalamine: >OD	10			
	Connolly[64,†]	Mesalazine: OD	NR	NR	UK	Cost (total and direct), ICER, QALY
		Mesalazine: BID	NR			

Notes: *Primary outcome; †economic study.
Abbreviations: ART, anti-retroviral therapy; BID, twice daily; HAART, highly active antiretroviral therapy; HIV/AIDS, human imunodeficiency virus/acquired immunodeficiency syndrome; ICER, incremental cost effectiveness ratio; ISMN, isosorbide mononitrate nitroglycerin; MEMS, medication event monitoring system; MPR, medication possession ratio; NR, not reported; OD, once daily; QID, four-times daily; SR, sustained release; TID, three times daily; QALY, quality-adjusted life year; XL, extended release.

Neurological disorders

Neurological disorders such as depression,[6,36,39,50] epilepsy,[51] and schizophrenia[52] were studied in six trials. Three studies in patients with depression[6,35,38] contributed adherence data for meta-analysis (Table 3). Random-effect meta-analysis showed that OD dosing was associated with nearly three times higher adherence compared with BID dosing (OR 3.10, 95% CI 2.15–4.47, $P < 0.001$, $I^2 = 82.9\%$).

Pfeiffer et al[52] demonstrated that a decrease in daily dosing frequency resulted in a small but significant increase in adherence measured using antipsychotic mean MPR change of 0.45 compared with −0.018 for schizophrenic patients without dosing frequency change ($P < 0.001$). Cramer et al[51] reported mean compliance rates of 87%, 81%, 77%, and 39% with antiepileptics prescribed as OD, BID, TID, and QID regimens, respectively. Overall, results of other empirical studies demonstrated that a decrease in daily dosage frequency was associated with increased adherence, compliance, or persistence (Table 2).[6,36,39,50]

Pain

There was little published evidence on adherence to treatments for pain. Two studies, one of which was observational[53]

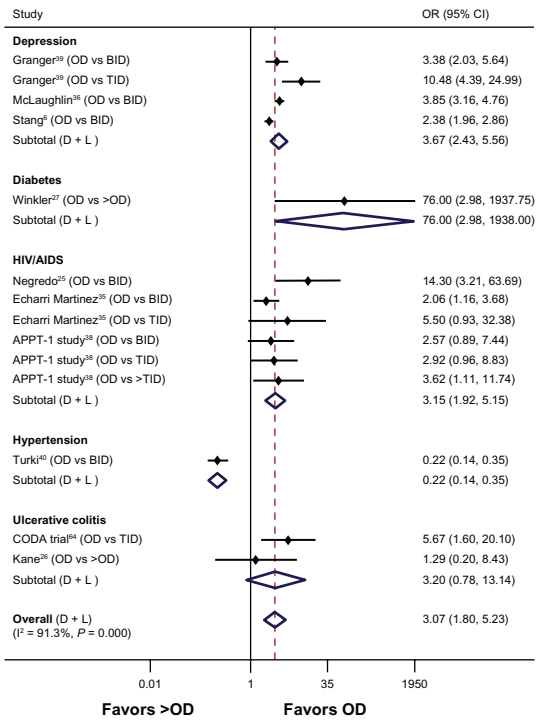

Figure 2 Forest plot of the odds ratios and 95% CIs for adherence rates associated with dosing schedules (once daily versus > once daily) of medications in all diseases.
Note: The broken line indicates overall effect relative to the comparator.
Abbreviations: BID, twice daily; CI, confidence interval; D + L, DerSimonian and Laird technique for meta-analysis; OD, once daily; OR, odds ratio; TID, three times daily; vs, versus; I^2, statistical heterogeneity.

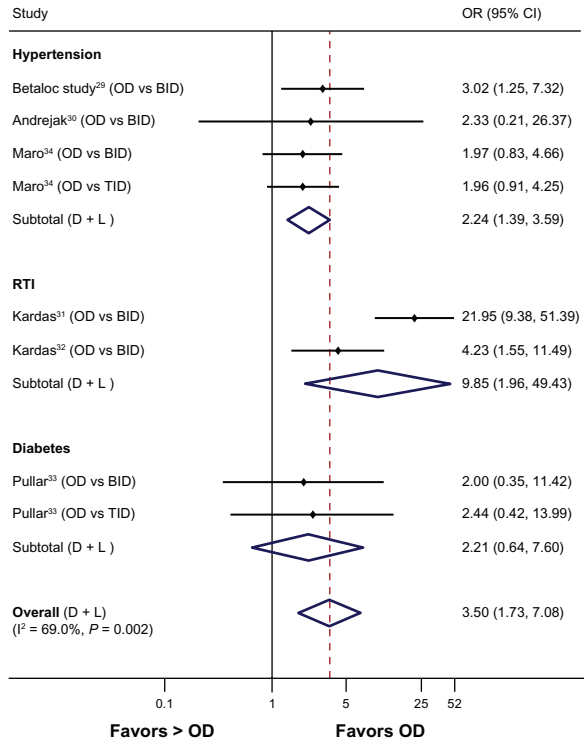

Figure 3 Forest plot of the odds ratios and 95% CIs for compliance rates associated with dosing schedules (once daily versus > once daily) of medications in all diseases.
Note: The broken line indicates overall effect relative to the comparator.
Abbreviations: BID, twice daily; CI, confidence interval; D + L, DerSimonian and Laird technique for meta-analysis; OD, once daily; RTI, respiratory tract infections; TID, three times daily; vs, versus; OR, odds ratio; I^2, statistical heterogeneity.

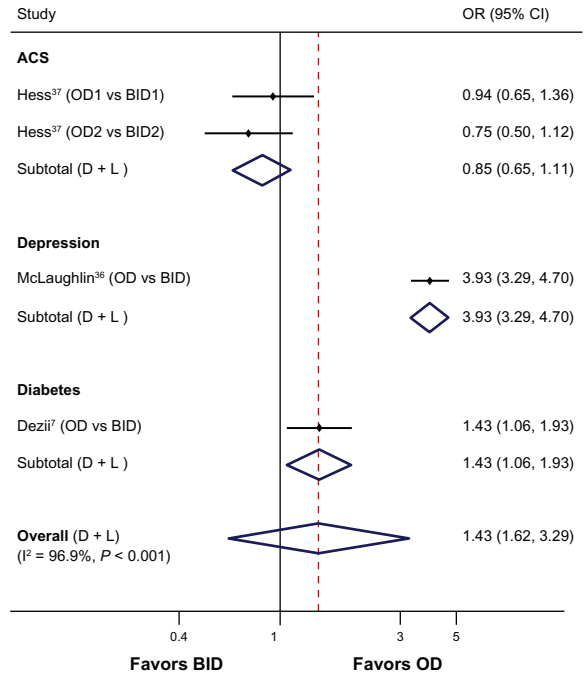

Figure 4 Forest plot of the odds ratios and 95% CIs for persistence rates associated with OD versus BID dosing schedules of medications in all diseases.
Note: The broken line indicates overall effect relative to the comparator.
Abbreviations: ACS, acute coronary syndrome; BID, twice daily; CI, confidence interval; D + L, DerSimonian and Laird technique for meta-analysis; OD, once daily; vs, versus; OR, odds ratio; I^2, statistical heterogeneity.

Table 3 Random effects meta-analyses for association of adherence/compliance/persistence to dosing schedules of medications in various chronic disorders

Disease	Dose comparison	OR (95% CI); *P*-value; heterogeneity
Adherence		
Depression	OD vs BID	3.10 (2.15–4.47); $P < 0.001$; $I^2 = 82.9\%$
Ulcerative colitis	OD vs >OD	3.20 (0.78–13.14); $P = 0.107$; $I^2 = 39.4\%$
	OD vs BID	3.48 (1.32–9.17); $P = 0.012$; $I^2 = 64.4\%$
HIV/AIDS	OD vs TID	3.48 (1.36–8.90); $P = 0.009$; $I^2 = 0\%$
	BID vs TID	1.38 (0.87–2.17); $P = 0.167$; $I^2 = 0\%$
Across all the diseases	OD vs BID	2.20 (1.09–4.41); $P = 0.027$; $I^2 = 95.5\%$
Across all the diseases	BID vs TID	1.88 (0.85–4.13); $P = 0.118$; $I^2 = 61.9\%$
Across all the diseases	OD vs >OD	3.07 (1.80–5.23); $P < 0.001$; $I^2 = 91.3\%$
Compliance		
Hypertension	OD vs BID	2.42 (1.33–4.40); $P = 0.004$; $I^2 = 0\%$
Infections	OD vs BID	9.85 (1.96–49.43); $P = 0.005$; $I^2 = 83.4\%$
Diabetes	OD vs >OD	2.24 (1.38–3.66); $P = 0.001$; $I^2 = 0.0\%$
Across all the diseases	OD vs BID	4.08 (1.68–9.91); $P = 0.002$; $I^2 = 73.4\%$
Across all the diseases	OD vs >OD	3.50 (1.73–7.08); $P < 0.001$; $I^2 = 69.0\%$
Persistence		
Cardiovascular disorders	OD vs BID	0.85 (0.65–1.11); $P = 0.235$; I^2 = N/A
Across all the diseases	OD vs BID	1.43 (0.62–3.29); $P = 0.405$; $I^2 = 96.9\%$

Abbreviations: AIDS, acquired immunodeficiency syndrome; BID, twice daily; CI, confidence interval; HIV, human immunodeficiency virus; I^2, statistical heterogeneity; N/A, not applicable; OD, once daily; OR, odds ratio; TID, three times daily; vs, versus.

and one that was economic,[54] provided data regarding compliance and costs associated with adherence to pain medications, respectively (Table 2). In the observational study,[53] patients on OD propranolol for treating migraine demonstrated higher mean compliance rates (79.8%) than those on BID atenolol (60.0%). Patients on BID atenolol in turn showed better compliance than TID pizotifen or TID methysergide (54.2%); however, the differences were not substantial.

An economic evaluation using a 3-month decision model of three first-line medications for diabetic peripheral neuropathic pain by Carlos et al[54] comparing duloxetine OD, pregabalin BID, and gabapentin TID demonstrated that in comparison to TID and BID, OD dosing was associated with a comparative cost savings of US$98 and US$129 per

Table 4 Studies presenting data on costs associated with adherence or compliance

Study	Disease	Type of evaluation	Results	Study conclusion
Brown[46]	Angina	Decision-analytic model	• Estimated total NHS annual cost for ISMN OD management: GB £248 • Estimated total NHS annual cost for ISMN OD management: GB £250	• Fewer health service resources were consumed by patients treated on OD regimen, with a higher compliance rate, compared to a BID regimen
Sidhu[9]	Renal transplant	Budget impact analysis	• Once daily tacrolimus yielded cumulative cost savings of GB £104,534	• Use of OD therapy could yield cost savings over five years in comparison to BID therapy of tacrolimus
Abecassis[61]	Renal transplant	Cost-effectiveness analysis	• Total direct cost with OD therapy: US$228,734 • Total direct cost with BID therapy: US$238,144	• Tacrolimus OD resulted in a reduction of costs relative to BID tacrolimus • Tacrolimus OD was the dominant therapy in the cost-effectiveness analysis

Note: 1 GBP = 1.5 USD.
Abbreviations: BID, twice daily; ISMN, isosorbide mononitrate nitroglycerin; OD, once daily dosing; NHS, UK National Health Service.

patient, respectively (Table 4). Incremental cost per QALY gained with OD over TID was US$8821 (over the patients dosing lifetime).

Diabetes

Five studies presented data on adherence, compliance, or persistence to medications in type 2 diabetes.[7,27,33,55,56] Random-effect meta-analysis for the assessment of compliance on data from two studies indicated OD dosing was associated with a significantly greater compliance rate compared with >OD dosing (OR 2.24, 95% CI 1.38–3.66, $P = 0.001$, $I^2 = 0.0\%$) (Table 3).[54,55] The remaining studies demonstrated that adherence rates varied with different assessment techniques; however, OD dosing had better adherence rates than BID/TID regimens.[7,26,32]

HIV infection

It was observed from six studies of antiretroviral treatments for HIV that regimens prescribed in a TID schedule were more likely to be missed compared with regimens prescribed less than TID.[8,25,35,38,57,58]

The results of random-effect meta-analysis from three studies in HIV patients indicated that the likelihood of being adherent was significantly higher with OD regimens compared with BID (OR 3.48, 95% CI 1.32–9.17, $P = 0.012$, $I^2 = 64.4\%$) and TID (OR 3.48, 95% CI 1.36–8.90, $P = 0.009$, $I^2 = 0\%$).[24,34,37] However, for the BID versus TID comparison, no statistically significant difference was observed (OR 1.38, 95% CI 0.87–2.17, $P = 0.167$, $I^2 = 0\%$) (Table 3).

Infections

Studies of infections included patients with respiratory tract infections (RTIs),[31,32] community-acquired pneumonia/acute bronchitis and streptococcal pharyngitis.[59,60] Random-effect meta-analysis on data from two studies assessing compliance to antibiotic therapy among patients with RTIs demonstrated that OD dosing was nearly ten times as likely to achieve compliance relative to BID (OR 9.85, 95% CI 1.96–49.43, $P = 0.005$, $I^2 = 83.4\%$) (Table 3).[31,32] For streptococcal pharyngitis, Raz et al[60] found a significant difference in compliance rates between BID (90%) and QID therapies (58%) ($P < 0.001$).

Spiritus et al[59] randomized patients with lower RTI to clarithromycin BID, erythromycin QID, or cefaclor TID. The authors in this study observed that the per-patient costs of health care resource utilization were US$191 for BID, US$264 for QID, and US$388 for TID (Table 4). Hospitalization costs were comparatively lower with BID (US$28,769 for 305 patients) compared with QID (US$73,322 for 316 patients) and TID (US$78,734 for 289 patients).[59]

Transplants

Two studies assessed the economic impact of adherence to immunosuppressants among patients undergoing kidney transplantation,[9,61] and one observational study evaluated compliance with interventions for liver transplantation.[62] Abecassis et al[61] modeled patient outcomes and treatment costs over 5 years for renal transplant comparing BID with OD tacrolimus (Table 4). Fewer patients were adherent to BID compared with OD immunosuppressants. Use of OD tacrolimus resulted in a reduction in 5-year discounted average patient total treatment costs relative to BID tacrolimus (US$228,734 versus US$238,144).[61] Similarly, Sidhu et al[9] calculated a 74% probability of adherence with OD versus 55% with BID tacrolimus (Table 4). Over 5 years, the OD regimen yielded cumulative cost savings relative to BID of £104,534, including savings in drug acquisition (£69,180), management of acute rejection episodes (£22,837), retransplantation (£417), and dialysis (£13,631).[9] Further, Eberlin and Kramer[62] demonstrated that switching patients from BID to OD tacrolimus-based regimen for liver transplantation resulted in a trend towards better compliance with OD regimen.

Ulcerative colitis

Three studies examined different dosing schedules of treatments for ulcerative colitis with adherence and persistence to medications,[26,28,63] and another study presented data on the associated economic impact (Table 2).[64] Random-effect meta-analysis on treatment adherence for ulcerative colitis indicated that OD dosing was associated with better adherence compared with >OD dosing (OR 3.20, 95% CI 0.78–13.14, $P = 0.107$, $I^2 = 39.4\%$).[25,27] Lachaine et al[63] reported that adherence and persistence to mesalazine formulations were relatively poor; however, improved adherence and persistence were observed with OD dosing.

Connolly et al[64] conducted an economic evaluation comparing OD with BID mesalazine based on results from an RCT (Table 4). Average annual costs per person treated with OD or BID mesalazine, including costs of treatment failure were £815 and £971, respectively, with an annual cost-savings (incremental cost per year) of £156 when using an OD regimen. OD had >0.95 probability of being cost-effective compared with BID based on accepted willingness to pay thresholds applied by the UK National Health Service.[64]

Discussion

Drug regimen complexity, ie, taking multiple daily doses of an intervention, is a critical factor affecting medication-taking behavior. The current analysis demonstrated that reducing the dosing regimen complexity improves adherence, compliance, and/or persistence. Across a variety of studied conditions, OD dosing of oral medications was associated with higher adherence compared with multiple-dosing schedules, which in turn may have led to decreased health care costs.

Our results are consistent with those found in empirical studies and literature reviews, including published meta-analyses, that showed adherence is inversely proportional to the number of medication doses per day.[15,16,18–20,65,66] A systematic review of 76 studies (1986–2000) by Claxton et al[16] to measure compliance found that simpler, less frequent dosing regimens resulted in better compliance across a variety of therapeutic classes. A review by Shi et al[15] of the effect of dose frequency on compliance between 1966 and 2006 showed that reducing dose frequency via new dosage forms and formulations may improve medication compliance. Similarly, the recent meta-analysis by Coleman et al[20] that included studies up to December 2011 found mean weighted adherence rates that were progressively lower as dosing frequency increased. The results of our quantitative analysis were also consistent with findings reported by other meta-analyses conducted specifically in the disease areas of hypertension and HIV infection.[18,19]

Economic evidence associated with adherence was reported in a variable manner; therefore, quantitative analyses were not possible. However, descriptive evaluation of the available evidence suggested less consumption of medical resources with OD dosing compared with BID dosing. More research is needed to quantify the extent and precision of the magnitude of effect.

This analysis could potentially be criticized for analyzing compliance and adherence seperately. However, our analysis was based on the terms used in the original studies, since ISPOR definitions consider these two terms to be synonymous.[12] In this regard, it should be noted that, although ISPOR definitions consider these two terms to be synonymous, differences have been noted in how these terms are used. Within the published literature, adherence has also been defined as a health plan constructed and agreed to by the patient in partnership with a health care provider in clinical decision making, while compliance implies a one-way relationship; the clinician dictates the medical regimen, and the patient is expected to comply.[67] A related limitation of this review is that the studies largely reported adherence based on patient self-report, rather than objective measures such as blood level monitoring, prescription refills, and electronic monitoring, making the studies subject to patient recall bias.[68] Nevertheless, despite these two limitations, there was general concordance of results between compliance and adherence in our analysis.

A meta-analysis can generate inherent biases when combining data from different studies with variable sample sizes, study designs, and outcome definitions. In our meta-analysis, all variables that could affect adherence, other than daily dose frequency, were assumed to be equal among comparators, which may not hold true in real-world settings. Data were combined from studies that used various definitions of adherence, compliance, and persistence, which is another limitation of this review. In addition, as persistence is a time-related event, studies assessing persistence used different methodologies and time points to assess this outcome. This difference was also reflected by the high heterogeneity associated with the meta-analysis results of overall persistence. However, random effects meta-analysis was employed to take into account heterogeneity due to potential confounding factors. Further, sensitivity analysis with respect to study designs to explore the impact of heterogeneity on the results revealed that higher adherence, compliance, and persistence were observed with OD versus > OD.

These results were consistent with the findings of other random-effects meta-analyses.

It should also be noted that some studies utilized different medications for the different dosing regimens. Thus, it is possible that there may have been factors other than the dosing frequency that may have contributed to the observed patterns of adherence/compliance, such as side-effects, size of tablet or capsule, taste, timing of administration (morning or evening, with or without food). While this may also represent a limitation of the current study, to our knowledge, factors that may relate to patient preference of medications and their impact on adherence, are rarely included in published studies and difficult to account for in such meta-analyses.

Knowing that poor treatment adherence/compliance/persistence is a problem in chronic pain patients, we found only two published studies addressing the relationship of adherence to treatment regimens in this population. Additional research is required to better characterize the nature and correlates of nonadherence (or noncompliance or nonpersistence) in patients being treated for chronic pain conditions. This lack of data also highlights the need for correlating adherence with economic outcomes in chronic pain. Although such a correlation was assessed in several other conditions, the overall paucity of studies investigating the impact of adherence on health care resource utilization and costs suggests that this represents an important research gap. An additional need is more detailed analysis of the relationship between dosing frequency and clinical outcomes.

Despite these limitations, there are several strengths to this review. The methodology involved was rigorous and followed stringent PRISMA guidelines. The effect of pooling different study designs and analysis types for examining overall adherence rates across different dosing schedules showed no evidence of bias in the results. The quantitative and descriptive evidence both indicated that the limitations considered did not change the overall observation that a reduction in dosing frequency resulted in better adherence, which may have contributed to a reduction in health care costs. Finally, our analysis was not limited to RCTs; rather, it included all published study designs.

Conclusion

Access to simplified dosage regimens by patients may be an important aspect in maximizing therapeutic success. The current meta-analysis suggested that the prescribed number of doses per day was inversely proportional to adherence/compliance/persistence across all acute and chronic conditions evaluated. In turn, poor adherence to medication regimens may result in greater consumption of medical resources, which in turn may lead to increased health care costs. Clinicians should be aware that medication adherence is a complex phenomenon with several factors at play and efforts to improve adherence should not be restricted to prescription of OD medications.[69,70] Other factors, including potency, tolerability, and risk of resistance to medications, in addition to patient's individual adherence patterns, are important considerations when selecting the optimal course of therapy for patients.

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Appendix

Appendix Study protocol listing the eligibility criteria for inclusion/exclusion of studies in the review as per the PRISMA guidelines

	Clinical effectiveness	Rationale
Inclusion criteria	Population • Age: Adults (≥ 18 years) • Gender: Any • Race: Any • Qualifying event/disease/factors: Any chronic disease	The population of interest to the review includes patients of any age, race, and gender receiving any oral medication for any chronic disease
	Intervention • Any oral intervention administered as OD, BID, TID, QID	The review aimed to compare adherence/compliance/persistence associated with different dosing regimens rather than any particular intervention
	Comparator • Any oral intervention administered as OD, BID, TID, QID	The comparator of interest was a different dosage regimen of the interventions being evaluated in the study. Since the review required direct evidence on adherence of dosing regimens of interventions, placebo/best supportive care (BSC) as comparators were not included
	Study design • Comparative cohort studies/longitudinal studies (retrospective) • Comparative cohort studies/longitudinal studies (prospective) • Published database analyses/registries • Case-control studies • Cross-sectional study—comparative • Randomized controlled trials • Non-randomized controlled trials • Economic studies	Observational studies and economic evidence were the best source of adherence/compliance data as they reflect 'real life' and were considered for the review.
	Language restrictions • English only	Studies with the full-text publication in English only were included in this review
	Publication timeframe • No date restriction for database searches	No date restriction was applied in order to capture the maximum amount of adherence data
Exclusion criteria	Outcome of interest • Studies that did not report the outcomes of interest (adherence/compliance/persistence and healthcare costs associated with non-adherence) were excluded from the review	Only studies reporting data pertaining to adherence/compliance/persistence and healthcare costs associated with non-adherence were included in the review
	Route of administration • Studies evaluating interventions administered via a non-oral route were excluded	Studies assessing interventions administered only through an oral route were included in the current review

Abbreviations: BID, twice daily; BSC, best supportive care; OD, once daily; QID, four times daily; TID, three times daily.

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