

Dosing frequency and adherence in chronic psychiatric disease: systematic review and meta-analysis

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Background: The purpose of this study was to investigate the impact of dosing frequency on adherence in severe chronic psychiatric and neurological diseases.

Methods: A systematic literature review was conducted for articles in English from medical databases. Diseases were schizophrenia, psychosis, epilepsy, bipolar disorder, and major depressive disorder.

Results: Of 1420 abstracts screened, 12 studies were included. Adherence measures included Medication Event Monitoring System (MEMS®), medication possession ratio, medication persistence, and refill adherence. Three schizophrenia and one epilepsy study used MEMS, and all showed a trend towards higher adherence rates with less frequent dosing regimens. Three depression and one schizophrenia study used the medication possession ratio; the pooled odds ratio of being adherent was 89% higher (ie, 1.89, 95% credibility limits 1.71–2.09) on once-daily versus twice-daily dosing. Two studies in depression and one in all bupropion patients assessed medication persistence and refill adherence. The pooled odds ratio for the two depression studies using medication persistence was 2.10 (95% credibility limits 1.86–2.37) for once-daily versus twice-daily dosing. For refill adherence after 9 months, 65%–75% of patients on once-daily versus 56% on twice-daily dosing had at least one refill. In all but one of the studies using other measures of adherence, adherence rates were higher with once-daily dosing compared with more frequent dosing regimens. No relevant studies were identified for bipolar disorder or psychosis.

Conclusion: Differences in study design and adherence measures used across the studies were too large to allow pooling of all results. Despite these differences, there was a consistent trend of better adherence with less frequent dosing.

Keywords: adherence, dosing frequency, schizophrenia, epilepsy, depression

Introduction

Chronic illnesses such as schizophrenia, epilepsy, and major depressive disorder (depression), are characterized by their need for long-term care and their severe impact on patients and their families, health care systems, and society. They affect a large proportion of the population; approximately 26.3 million people have schizophrenia¹ and around 50 million have epilepsy worldwide,^{2,3} while in most countries 8%–12% of all inhabitants are estimated to suffer from depression in their lifetime.^{4,5} Disease management with long-term treatment includes the use of typical or atypical antipsychotic medication for schizophrenia, antiepileptics for epilepsy, and antidepressants (often with psychotherapy and counseling) for depression. Because these disorders are chronic and/or relapsing, adherence to prescribed drug therapies is a key to

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relapse prevention and sustained treatment success. The term adherence describes the extent to which a patient takes medication as prescribed with respect to dosage and dosing intervals.⁶

Nonadherence can have considerable negative clinical and economic consequences. For instance, patients with schizophrenia who discontinue antipsychotic medication are at increased risk of symptom exacerbation and poor functional outcomes, as well as relapse and hospitalization.⁷ In one recent review evaluating adherence in schizophrenia, patients with schizophrenia receiving antipsychotic medication took less than 60% of their prescribed dose, and up to 75% of patients were noncompliant by the second year of treatment.⁸ Medication nonadherence was the strongest predictor of relapse, with an odds ratio of 7.6.⁹

In epilepsy, adherence to antiepileptic medication is critical in preventing or minimizing seizures.¹⁰ Increased seizure frequency can have serious repercussions on quality of life,^{2,3} as well as increased utilization and costs for inpatient and emergency services.^{11–13} In depression, 28% of patients on antidepressant medication discontinued use within the first month and at least 40% by 3 months in a major depressive disorder study.¹⁴ That study also found early drug discontinuation to be associated with a 77% increase in the risk of relapse, which ultimately resulted in higher health care costs.¹⁴

Nonadherence can be intentional, due to patients' own poor expectations of treatment, side effects, or lifestyle choice, or not intentional, when patients fail to adhere through forgetfulness, misunderstanding, or uncertainty about clinicians' recommendations. A wide range of factors affect adherence, and can be classified into disease-related drivers, patient-related drivers, treatment-related drivers, and environment-related drivers. Therefore, a wide range of methods has been used to assess adherence in various studies.

Dosing complexity (or increased dosing frequency) may contribute to poor medication adherence in chronic illnesses such as schizophrenia, epilepsy, and depression. The assumption that once-daily dosing improves a patient's adherence to therapy compared with more frequent daily dosing regimens has been studied in prospective studies (eg, using pill count^{15,16} or Medication Event Monitoring System [MEMS®]^{15–18} as well as retrospective database studies eg, using the medication possession ratio [MPR]^{19–22} and drug persistence).^{19,21,22} Efforts to provide greater objectivity and uniformity in measuring adherence have led to the use of MEMS, a medication bottle cap with a microprocessor that records the occurrence and time of each bottle opening, which has been used in several mental health studies (ie,

in schizophrenia,^{16–18,23} depression,^{23,24} and Parkinson's disease)²⁵ as well as for other medical conditions (ie, for AIDS,²⁶ hypertension,²⁷ and liver transplantation).²⁸

Given that improving adherence is clinically highly relevant, and simplifying dosing schedules is seen as one way to meet this end, a systematic review of the link between dosing frequency and adherence is warranted. To our knowledge, no such systematic review currently exists. Specifically, there are no assessments of the pooled quantitative effect of increased dosing frequency on adherence. The primary objective of this study was to perform a systematic literature review to assess the relationship between dosing frequency (specifically once-daily versus multiple daily dosing) and adherence (irrespective of how it was measured) in patients with chronic psychiatric and neurological diseases in the form of schizophrenia, psychosis, epilepsy, depression, and bipolar disorder. A secondary objective was to pool the results in a meta-analysis, if possible.

Materials and methods

A systematic search of the literature was conducted for English language articles in MEDLINE, MEDLINE In-Process (MEIP) and EMBASE (using OVID) and the Cochrane Library (CCTR [Central Register of Controlled Trials] and DARE [The Database of Abstracts of Reviews of Effects]). No date restrictions were applied to the search. The search used free text and MeSH terms to identify studies in the following diseases: schizophrenia and disorders with psychotic features, psychosis, epilepsy, bipolar disorder, and major depressive disorder (depression). The disease terms were then combined with terms for the outcomes of interest, which were adherence/compliance/persistence and dosing frequency. Given an expected paucity of data on this topic, no restriction was applied as to specific measurements of adherence. The search did not include abstracts from conferences. The search was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic literature reviews and meta-analysis. The search strategy (OVID) is presented in Table 1.

Abstracts were screened by two researchers independently for relevance to this study. Full-text publications that were potentially relevant were then screened for inclusion against the following predetermined criteria:

- Population (chronic psychiatric and neurological diseases [see above], adults)
- Interventions (oral treatments)
- Comparison treatments (once a day versus multiple times daily)

Table I Search strategy (OVID)**Search strategy: MEDLINE, MEIP, EMBASE**

1. Patient compliance/(109960)
2. Patient compliance/or medication adherence/or treatment refusal/(128261)
3. Treatment compliance/or treatment refusal/(86676)
4. (Adherence or compliance or medication persistence or non-adherence or non-compliance or adhere\$ or complian\$ or non?adhere\$ or non?complan\$ or comply or patient compliance).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui] (424591)
5. 1 or 2 or 3 or 4 (438525)
6. (Drug\$ frequen\$ or drug\$ schedule\$ or drug\$ regime\$ or medication\$ frequen\$ or medication\$ schedule\$ or medication\$ regime\$ or dos\$ frequen\$ or dos\$ schedule\$ or dose regime\$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui] (62836)
7. ((Drug\$ or medication\$ or dos\$) adj2 (frequen or schedule\$ or regime\$)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui] (159500)
8. Drug dose regimen/(24760)
9. Drug dosages/(0)
10. (Drug dose regimen or drug dosages).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, ui] (25699)
11. 6 or 7 or 8 or 9 or 10 (162863)
12. "Schizophrenia and disorders with psychotic features"/or psychotic disorders/or exp schizophrenia/(201450)
13. Schizophrenia/or psychosis/(175253)
14. Epilepsy/(107976)
15. Bipolar disorder/(44505)
16. Depressive disorder, major/(35411)
17. Major depression/(21585)
18. Depressive disorder/or depressive disorder, major/(247165)
19. ("Schizophrenia and disorders with psychotic features" or psychosis or psychotic disorders or epilepsy or bipolar disorder or depressive disorder).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, ps, rs, nm, an, ui] (374712)
20. 12 or 13 or 19 or 14 or 15 or 16 or 17 or 18 (635982)
21. 5 and 11 and 20 (1240)
22. Limit 21 to English language (1148)
23. Limit 22 to human (1111)
24. Limit 23 to humans (1111)
25. Remove duplicates from 24 (918)

Note: A simplified search was carried out in the Cochrane Library (Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects).

Abbreviation: MEIP, MEDLINE In-Process.

- Outcomes (medication compliance, adherence, or persistence rates)
- Study design (prospective or retrospective observational studies, randomized clinical trials [Phase II or III], or meta-analyses).

The feasibility of pooling results in a meta-analysis was assessed based on the similarity of study designs, patient characteristics, and definition of outcomes used. In the case of large differences, a qualitative comparison was made instead. For mixed treatment comparison, a fixed-effects model^{29,30} or a random-effects model^{29,30} can be used. The fixed-effects model assumes that the differences in estimated relative treatment effects across studies in the network of evidence are only caused by random variation. The random-effects model assumes that the differences in estimated relative treatment effects are caused by random variation as well as by variation in the true treatment effect.

For the quantitative analyses, a fixed-effects model for mixed treatment comparison was used because this was the most appropriate model for analyzing a small number of studies. Random effects models were not used due to the limited number of studies (ie, two to four studies depending

on the scenario). Odds ratios were calculated for certain adherence measures (eg MPR) where they were not reported in the original publication. Several scenario analyses were performed with inclusion of different patient populations. For each scenario, the pooled odds ratio (OR) was calculated, together with the corresponding 95% credibility limits (CrL) as a measure of uncertainty.

Results

Identification of studies

The OVID and Cochrane Library searches (CCTR and DARE) identified 1379 abstracts in total. Forty-one abstracts that were published separately were manually added. Of the 1420 abstracts that were screened, 42 potentially relevant full-text publications were selected for a second screening, and 12 full papers were included in the final review. Figure 1 presents the flow chart of identified studies.

Assessment of included studies

The studies included were compared in terms of adherence outcomes used, patient population, study design, and dosing frequency comparisons. An overview of the different

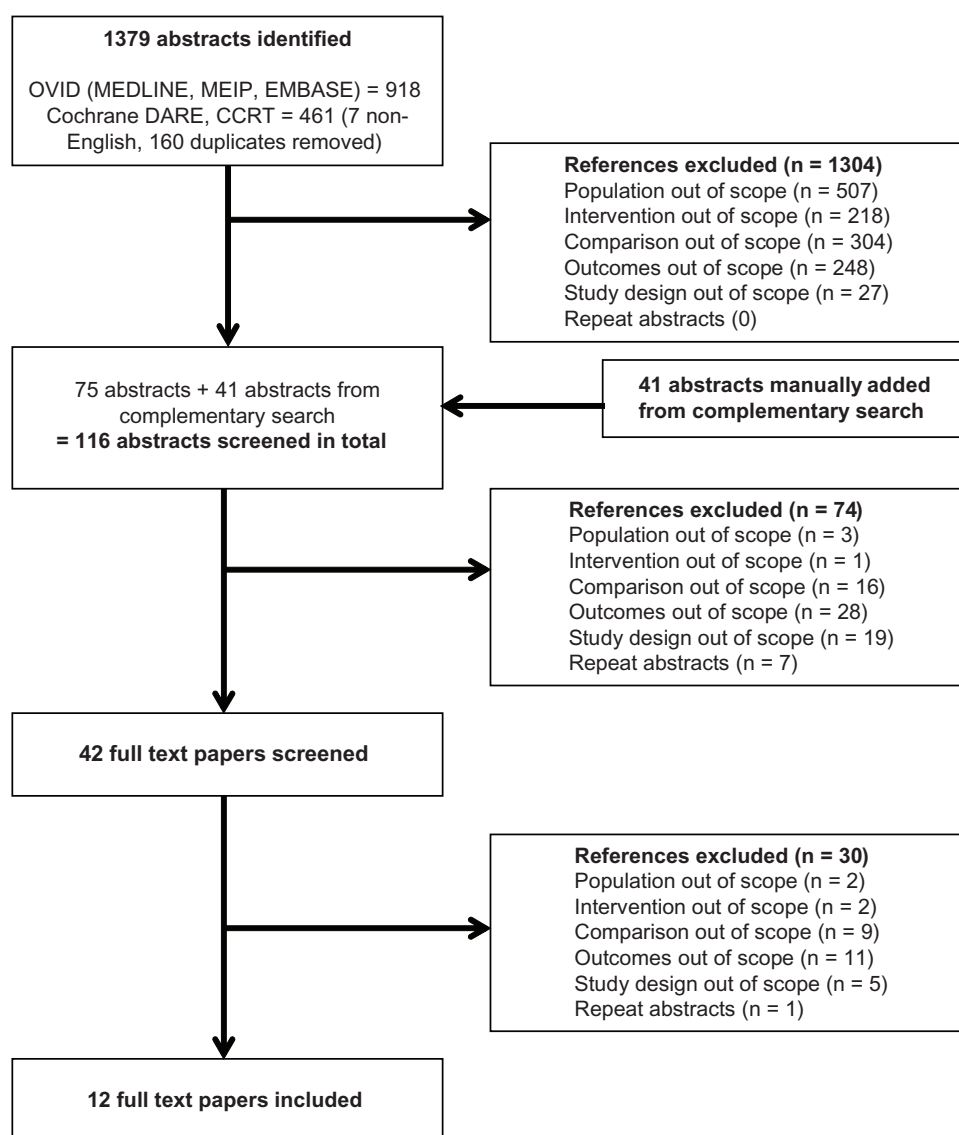


Figure 1 Flowchart of identified studies.

Abbreviations: MEIP, MEDLINE In-Process; DARE, The Database of Abstracts of Reviews of Effects; CCRT, Cochrane Central Register of Controlled Trials.

adherence measures and associated studies is found in Table 2, whereas Table 3 provides a detailed presentation of study characteristics and main outcomes.

Various adherence outcome measures were used (Table 2). Four studies^{15–18} reported the results recorded by MEMS. Four studies^{19–22} reported MPR of which three studies also reported refill adherence^{19,21,22} and medication persistence.^{19,21,22} Another four studies used a different outcome measure that did not allow further comparison: Doughty et al³¹ used four questions to assess levels of adherence (eg, “never miss a dose” to “miss once a week or more”); Zaccara et al³² compared mean drug plasma levels with different dosing frequencies; Cramer et al³³ assessed the odds of missing a dose with different dosing frequencies; and Meier et al³⁴ used the Medication Adherence Questionnaire (MAQ) and Clinician

Rating Scale (CRS) to assess adherence. Remington et al¹⁶ used clinician rating as a measure of adherence.

In terms of patient populations, there were four studies in epilepsy,^{15,31–33} five studies in schizophrenia,^{16–18,20,34} and three studies in depression^{19,21,22} (although one of these evaluated any patient treated with bupropion extended release (XL) or sustained release (SR) which may have included other conditions²¹). The mean patient age was fairly comparable across studies, ranging from 35 to 45 years, except for one study in schizophrenia in which patients had a mean age of 55 years.²⁰ Looking at the gender distribution of patients in the trials, the majority of patients in the depression studies^{19,21,22} were women (around 64%–70%) compared with the epilepsy studies,^{15,31–33} where approximately half of the population were women (50%–53%). Two epilepsy^{15,33} studies did not report

Table 2 Overview of different adherence measures per study

Adherence measure	Study	Disease and study design	Definition of adherence measure
MEMS®	Byerly et al ¹⁸	Schizophrenia Prospective study	MEMS definition < 70% then nonadherent
	Diaz et al ¹⁷	Schizophrenia Prospective study	Number of bottle openings over the number of prescribed openings in the 3-month period
	Remington et al ¹⁶	Schizophrenia Prospective study	No definition
	Cramer et al ¹⁵	Epilepsy Prospective study	80% threshold when adherence treated as dichotomous
	Pfeiffer et al ²⁰	Schizophrenia Retrospective database analysis (change in MPR was used as measure)	As a continuous variable from 0%–100% Definition of noncompliance was omission of a scheduled dose; MEMS was used to observe pill-taking habits
MPR		Depression Retrospective database analysis	MPR (number of days supply from Rx that year)/(number of noninstitutionalized days in that period); MPR of 1 = full adherence; MPR of 0.5 = patients received 50% of medication needed for continuous use
	McLaughlin et al ¹⁹	Depression Retrospective database analysis	MPRs were calculated as (sum of days supply for all filled prescriptions)/(study period = 270 days), with days of supply for any prescription at end of the study period truncated at day 270 from the index date
	Stang et al ²²	Depression Retrospective database analysis	MPR was calculated as the sum of the number of days of supply for all filled prescriptions, divided by the number of days in the study period; the number of days of supply for any prescription at the end of the study period was truncated at day 270 from the index date in these calculations; the likelihood of having a MPR > 0.7 was considered to reflect adherence
	Stang et al ²¹	Depression retrospective database analysis	MPR was determined for patients who filled at least 2 prescriptions for bupropion XL or bupropion SR
Persistence	McLaughlin et al ¹⁹	Depression Retrospective database analysis	Medication persistence was defined as (interval between first and last prescription claims)/(study period = 270 days)
	Stang et al ²²	Depression Retrospective database analysis	Medication persistence was calculated as the interval in days between the first and last prescription claims, divided by the number of days in the study period
	Stang et al ²¹	Depression Retrospective database analysis	Patients were considered to be persistent during the times that they refilled a bupropion prescription within twice the number of days of supply of the previous prescription
	McLaughlin et al ¹⁹	Depression Retrospective database analysis	Refill adherence, presented as a categorical measure of the percentage of patients remaining on therapy as measured by the number of refills a patient had for the index medication during the study period
Refill adherence	Stang et al ²²	Depression Retrospective database analysis	Refill adherence was calculated as a categorical measure of the percentage of patients remaining on therapy as measured by the number of refills a patient had for the index medication during the study period
	Stang et al ²¹	Depression Retrospective database analysis	Refill adherence over time was calculated as the percentage of patients with ≥ 1, 2, 3, 4, 5, and 6+ refills from October 2004 to October 2005
	Doughty et al ³¹	Epilepsy Survey study	Adherence: 1, never miss; 2, miss less than once per month; 3, miss more than once per month; 4, miss once a week or more
Four-item questionnaire	Zaccara et al ³²	Epilepsy Retrospective study	No definition
Mean drug plasma level	Cramer et al ³³	Epilepsy Survey study	Odds of missing a dose per different dosing regimen
Odds of missing dose	Cramer et al ¹⁵	Epilepsy Survey study	Pill count: (total number of doses observed/number of doses prescribed *number of days observed)* 100

(Continued)

Table 2 (Continued)

Adherence measure	Study	Disease and study design	Definition of adherence measure
MAQ self-report	Remington et al ¹⁶	Schizophrenia Prospective study	No definition; 80% threshold when adherence treated as dichotomous; as a continuous variable from 0% to 100%
	Meier et al ³⁴	Schizophrenia Survey study	MAQ consists of self-report of four yes/no questions; result ≥ 4 points reflects good adherence, and <4 points insufficient adherence
Self-report	Remington et al ¹⁶	Schizophrenia Prospective study	No definition; 80% threshold when compliance treated as dichotomous, as a continuous variable from 0% to 100%
	Meier et al ³⁴	Schizophrenia Survey study	Clinician or key worker estimated patient adherence on a scale from 1 to 7 points, with ≥ 5 good adherence and <5 insufficient adherence
CRS	Remington et al ¹⁶	Schizophrenia Prospective study	No definition; 80% threshold when adherence treated as dichotomous

Abbreviations: MEMS®, medication event monitoring system; MPR, medication possession ratio; MAQ, medication adherence questionnaire; CRS, clinician rating scale; Rx, prescription.

the number of women. The proportion of women in depression studies was high when compared with the schizophrenia^{16,18,20,34} studies where women were in a minority (5%–50%), while Diaz¹⁷ did not report the number of women.

Study design varied according to the adherence outcome measure used. The four studies assessing MEMS^{15–18} were small prospective studies which included between 25 and 100 patients, with a follow-up period of 1–4.5 months. The four studies assessing MPR^{19–22} (including three assessing refill adherence^{19,21,22} and persistence)^{19,21,22} were large retrospective US database studies with patient numbers between 2991 and 269,517 and study periods of 9 months to one year. The four remaining studies^{31–34} were international studies that applied various adherence measures and included small and large studies and surveys, as well as retrospective and prospective designs.

Most of the studies were conducted in the US,^{15–24} one study was performed in Canada,¹⁶ one was performed in Italy,³² two were international studies (one was performed in four countries [The Netherlands, United Kingdom, Italy and Germany],³⁴ and the other was performed in eight countries [Germany, Bulgaria, Hungary, Latvia, Romania, Russia, Spain, and India]).³¹

Four studies^{18,19,21,22} compared once-daily dosing with twice-daily dosing; six studies^{15–17,32–34} compared once-daily with twice-daily dosing, three times daily, or four times daily dosing; a schizophrenia study²⁰ compared once-daily with more than once-daily dosing; and a study in epilepsy³¹ compared once-daily versus twice-daily and more than twice-daily dosing.

Definitions of adherence measures used

The following adherence measures were used in more than one study and allowed comparisons to be made. MEMS measured the number of bottle openings during a given time period so that the proportion of the prescribed or expected number of bottle openings that actually occurred could be estimated. A patient was arbitrarily deemed to be nonadherent in the studies if the MEMS score was under 70%,¹⁸ under 80%,¹⁶ or if a scheduled dose was omitted.¹⁵ Because the study duration varied and longer duration studies are expected to have worse adherence outcomes, the period over which MEMS scores were assessed was not comparable.

MPR estimated the days of medication supply the patient has taken for the duration prescribed or required. A MPR of 1.0 indicates full adherence,³⁵ whereas an MPR of 0.5 indicates that a patient has taken half of the medication needed to ensure continuous use.³⁵ All studies^{19–22} used similar definitions of MPR.

Table 3 Characteristics of studies included

Study	Population	Study design	Outcome measure and comparison	Result (mean \pm SD)
Byerly et al ¹⁸	Schizophrenia Mean age 39.2 \pm 8.6 years Females 28%	n = 25 patients (22 QD, 3 BID) Prospective study Follow-up 3 months	MEMS [®] QD versus BID	MEMS: QD 78.2% \pm 18.1% versus BID 66.2% (SD not reported)
Diaz et al ¹⁷	Schizophrenia Mean age 34.1 \pm 9.2 years Female 27%	n = 49 patients (17 QD, 30 BID, 2 TID) Prospective study Follow up 3 months	MEMS QD versus BID, TID	MEMS: QD 62% \pm 39% versus BID 26% \pm 28% versus TID 22% \pm 30%
Remington et al ¹⁶	Schizophrenia Mean age 36 \pm 10.3 years Females 50%	n = 52 patients Prospective study Follow-up 1 month	MEMS QD versus BID, TID Pill count Self-report Clinician rating	PANSS total score (β = -0.429; P = 0.001) and dosing complexity (β = -0.246, P = 0.054) were significant predictors of adherence (defined using MEMS scores) MEMS: QD 87%; BID 81%; TID 77%; QID 39% Pill count: QD 99%; BID 92%; TID 91%; QID 90%
Cramer et al ¹⁵	Epilepsy Age range 18–68 years Females 50% (of 24 patients using MEMS)	n = 26 patients Prospective study Follow up 4.5 months	MEMS QD versus BID, TID, QID Pill count	MEMS: QD 87% \pm 11% versus BID 81% \pm 17% versus TID 77% \pm 12% versus QID 39% \pm 24%
Pfeiffer et al ²⁰	Schizophrenia Mean age of QD group 56.1 \pm 11.4; >QD 55.3 \pm 10.7 years Females 5%	n = 32,612 patients Retrospective database analysis Follow-up one year	Change in MPR QD versus >QD	Pill count: QD 99%; BID 92%; TID 91%; QID 90% Decrease from >QD to QD: MPR change 0.045 (P < 0.001) Increase from QD to >QD: MPR change -0.105 (P < 0.001) Stable QD and stable >QD: mean MPR 0.80
McLaughlin et al ¹⁹	Depression Mean age of QD group 45.1 years and BID group 46.5 years Females QD 70%, BID 71%	n = 3138 patients Retrospective database analysis Follow-up 9 months	MPR Persistence Refill adherence QD versus BID	MPR: QD 0.52 \pm 0.35 versus BID 0.35 \pm 0.26 (P < 0.001) Persistence: QD 0.5 \pm 0.4 versus BID 0.32 \pm 0.33 Refill: QD 65% had \geq 1 refill and 26% had \geq 6 refills versus BID 57% had \geq 1 refill, and 14% had \geq 6 refills
Stang et al ²²	Depression Mean age: QD group, 40.77 years; BID group, 40.91 years Female QD 64%, BID 63%	n = 2991 patients Retrospective database analysis Follow-up 9 months	MPR Persistence Refill adherence QD versus BID	MPR: QD 0.50 \pm 0.33 versus BID 0.36 \pm 0.31 (P < 0.0001) Persistence: QD 0.47 \pm 0.38 versus BID 0.30 \pm 0.36 (P < 0.0001) Refill: QD 75.3% had \geq 1 refill and 31.4% had \geq 5 refills versus BID 55.4% had \geq 1 refill, and 18.7% had \geq 5 refills (P < 0.05)
Stang et al ²¹	Depression Rx for bupropion XL or SR Mean age QD 42.6 years for females and 42.3 for males; BID group 47.3 years for females and 45.0 years for males Females QD 69%, BID 67%	n = 269,517 patients Retrospective database analysis Follow-up 9 months	MPR Persistence Refill adherence QD versus BID	MPR: QD (0.26) versus BID (0.16) Persistence: QD significantly more likely to refill a Rx versus SR (Kaplan-Meier curves, P < 0.0001, log-rank test) Refill over 1 year: QD 60.1% had \geq 1 refill versus BID 51.3% (P < 0.0001). QD 25.3% had \geq 6 refills versus BID 9.5%
Dougherty et al ³¹	Epilepsy Mean age 33 (range 16–92) years Females 53%	n = 2031 respondents Survey study Follow-up 3 months	Four-item questionnaire QD versus BID, >BID	Less frequent dosing regimens had better reported adherence Prefer to take antiepileptic QD (time 1 [at time of inclusion] 88%; time 2 [3 months after study inclusion] 89%) It is more convenient to take antiepileptic only QD (time 1, 92%; time 2, 93%) Would be less likely to forget to take antiepileptics if I only had to take it QD (time 1, 81%; time 2, 80%); taking antiepileptics QD only would fit in better with my lifestyle (time 1, 84%; time 2, 87%)

(Continued)

Table 3 (Continued)

Study	Population	Study design	Outcome measure and comparison	Result (mean ± SD)
Zaccara et al ³²	Epilepsy	n = 49 patients	Mean drug plasma levels	Higher plasma drug levels for less frequent dosing regimens ($P < 0.001$)
	Mean age: DPH, 34.4 ± 13.7 years; PH, 35.4 ± 16.7 years	Retrospective study	BID versus TID, QID	
Cramer et al ³³	Females 51%	Follow-up not reported	QD versus BID, TID, QID	Odds of missing a dose increase by 27% for each increase in number of times per day medication was required (eg, 1, 2, 3, 4 times daily)
	Epilepsy	n = 670 respondents	Odds of missing dose	
Meier et al ³⁴	Mean age not reported	Survey study	QD versus BID, TID, QID	Patients with QD regimen had worse adherence than patients with BID regimen
	Female, % not reported	Follow-up not reported	MAQ self-report and CRS	
	Schizophrenia	n = 409 patients	QD versus BID versus TID	Mean MAQ sum score 2.97 ± 1.21
	Mean age 41.5 ± 11.5 years	Survey study	versus more than TID	
	Females 40%	Follow-up not reported		Mean CRS 5.25 ± 1.37

Abbreviations: MEMS, medication event monitoring system; MPR, medication possession ratio; MAQ, medication adherence questionnaire; CRS, clinician rating scale; QD, once-daily; BID, twice-daily; TID, three times a day; QID, four times a day; PANSS, positive and negative syndrome scale; Rx, prescription; DPH, diphenylhydantoin; PH, phenobarbital; SD, standard deviation.

Medication persistence assessed the long-term continuation of medication as the interval between first and last prescription claims divided by the study period^{19,22} or if a prescription was refilled within a given period (eg, allowing a grace period between supply ending and refilling prescription).²¹

Refill adherence assessed the proportion of patients remaining on treatment by the number of prescription refills during the study period.^{19,22} Satisfactory refill adherence was defined as dispensed refills covering 80%–120% of the prescribed treatment time. Refill adherence levels below 80% were referred to as undersupply and those over 120% as oversupply.^{36,37}

Results by endpoint

The results are presented for adherence endpoints used in multiple studies, and data were pooled where feasible. The individual study results are presented in Table 3.

MEMS

MEMS was included as an outcome measure in three studies of schizophrenia^{16–18} and one study of epilepsy.¹⁵ One study in schizophrenia¹⁸ performed statistical analyses, but did not control for confounders, while another study in schizophrenia¹⁷ performed statistical analyses and found that gender and random versus nonrandom design were effect modifiers. The third schizophrenia study¹⁶ performed two separate multivariate analyses to control for the overlapping influence of various predictors on adherence. A linear regression analysis showed that, when adjusting for the variability of other explanatory variables (confounders), only the Positive and Negative Symptom Scale total score and dosing complexity remained as significant predictors of adherence. A discriminant function analysis found that Positive and Negative Symptom Scale total score, dosing complexity, and duration of illness were variables with significant discriminant weights.¹⁶

Although two schizophrenia studies^{17,18} had similar study designs and patient populations, they reported adherence values of 66.2%¹⁸ and 26%.¹⁷ This difference might be explained by the fact that the group in which adherence was 26%¹⁷ was based on a sample of only three patients¹⁷ and therefore the results may not be reliable. In the third schizophrenia study using MEMS with a commonly used threshold for adherence of 80%, 48% of patients were considered adherent.¹⁶ Despite study differences, the findings for once-daily versus multiple daily dosing regimens were consistent, in that the dosing regimen was a strong predictor of adherence, meaning that patients on once-daily regimens had better adherence than those on twice-daily regimens.

The mean adherence rate per patient was also reported in one study¹⁶ because the authors questioned the validity of using a cutoff of 80% for adherence. The mean adherence rate using MEMS was 66.12% \pm 31.00%. Dosing complexity was again a significant predictor of adherence as measured by MEMS.¹⁶ The epilepsy study reported adherence outcomes at 4.5 months follow-up and found similar trends, ie, 87% (once-daily dosing) versus 81% (twice-daily dosing) versus 77% (three times daily) and versus 39% (four times daily,¹⁵ $P < 0.05$). In all studies using MEMS as an outcome measure, there was a consistent trend showing higher adherence rates with less frequent dosing regimens, irrespective of the study duration or disease. The small patient numbers and lack of data did not allow more detailed analyses.

Medication possession ratio

MPR was included as an outcome measure in three studies for depression^{19,21,22} (of which one study included a broader population of any patient receiving bupropion XL or SR)²¹ and one study for schizophrenia.²⁰ Data from depression studies^{19,22} were pooled because these were comparable in terms of study design, population, and outcomes. Both studies reported MPR values of around 50% for once-daily versus 35% for twice-daily dosing, implying an unadjusted OR of 2.01¹⁹ and 1.78,²² and therefore concluded that patients receiving once-daily medication were significantly more likely to remain on their medication than those receiving twice-daily medication. Both papers concluded that there were no differences in adherence level for different genders, while age and index date were effect modifiers.

The pooled OR was 1.89 (95% CrL 1.71–2.09, Table 4) using a fixed-effects model. This meant that the odds of being adherent was 89% higher for patients on a once-daily versus twice-daily regimen. The third depression study, which included a broader mix of patients, found lower MPR values but a greater adherence rate for once-daily versus twice-daily regimens.²¹ A similar conclusion was reached by Stang et al,²¹

where effect modifiers were gender, having insurance, having authorized refills, remaining in the current prescription, having a repeat refill for the current prescription, and having a large number of total days of supply in the past year.

The schizophrenia study found higher MPR values for stable patients on any dosing regimen. MPR adherence significantly improved for patients who decreased to once-daily dosing, and worsened for patients who increased from once-daily to multiple daily dosing compared with their stable counterparts.²⁰ The study concluded that for patients on stable dosing frequencies, the MPR before the dose change, and the demographic and clinical characteristics described previously, had little influence on the adherence rates.²⁰

Persistence

Studies assessing medication persistence included two^{19,22} studies in depression and one²¹ in a broader population on bupropion XL or SR. In a retrospective database analysis, once-daily bupropion was associated with an average additional 44 days on therapy over the 9-month follow-up period, and an additional 28% of patients being adherent.¹⁹ Both studies in depression^{19,22} reported a significant difference in persistence results for once-daily (around 50%) versus twice-daily (30%) dosing. Both papers concluded that there were no differences in adherence levels for different genders, while age and index date were effect modifiers.^{19,22}

The study²¹ identified effect modifiers as gender, having insurance, having authorized refills, remaining in the current prescription, having a repeat refill for the current prescription, and having a great number of total days of supply in the past year.²¹

All three studies^{19,21,22} imply a similar calculated persistence OR for once-daily versus twice-daily dosing (OR 2.13, 95% CrL 1.78–2.53;¹⁹ OR 2.07, 95% CrL 1.75–2.45;²² and OR 2.07, 95% CrL: not applicable).²¹ By pooling the results for the two depression studies,^{19,22} an OR of 2.10

Table 4 Pooled results for adherence by medication possession ratio: odds ratios (95% CrL) of once-daily versus twice-daily regimens

Description	Pooled OR, QD versus BID (95% CrL)
Two ^{19,22} retrospective database analysis studies in depression	1.89 (1.71–2.09)
Three retrospective database analysis studies, two ^{19,22} in depression and one ²⁰ in schizophrenia	1.89 (1.71–2.09)
Four retrospective database analysis; two studies in depression, ^{19,22} one ²⁰ in schizophrenia, and one ²¹ that included a broader patient population who used bupropion	1.84 (N/A)
One ²⁰ retrospective database analysis in schizophrenia	2.15 (1.53–3.22) patients on initially QD 3.06 (2.05–5.12) patients on initially more than QD

Note: *OR were calculated from data presented in the study in scenario 4.

Abbreviations: BID, twice daily; CrL, credibility limits; OR, odds ratio; QD, once daily.

(95% CrL 1.86–2.37) was estimated. This means that the odds of patients on once-daily regimen being adherent was more than twice the odds of patients being adherent on twice-daily dosing.

Refill adherence

Studies assessing refill adherence included two studies in depression^{19,22} and one in a broader population²¹ on bupropion XL or SR. All three studies assessed the proportions with at least one refill during the study period, two studies assessed the proportion of at least six refills,^{19,21} and one study assessed the proportion of at least five refills,²² and study periods ranged from 9 months to one year. For the studies of 9 months' duration, the proportion of patients with at least one refill was 65%–75% on once-daily^{19,22} versus around 56% on twice-daily^{19,22} dosing. For the one-year mixed population study, around 60% on once-daily versus 51% on twice-daily regimens had at least one refill ($P < 0.0001$).²¹ This study with a mix of populations²¹ found a similar trend of calculated refill adherence with QD (39%) versus BID (24%) regimens. Because adherence is expected to decrease over time, the studies assessed the proportions of patients with multiple refills during the study period. The proportion of patients with at least 5–6 refills was around 26%–31% for once-daily^{19,22} versus 14%–19% for twice-daily^{19,22} regimens over 9 months, and was 25% for once-daily²¹ versus 10% for twice-daily²¹ regimens over one year. The studies in patients with depression only conclude that there were no differences in adherence levels for the different genders, while age and index date were effect modifiers.^{19,22} A similar conclusion was reached by Stang et al,²¹ where effect modifiers were gender, having insurance, having authorized refills, remaining in the current prescription, having a repeat refill for the current prescription, and having a great number of total days of supply in the past year.

Other measures of adherence

In addition to the four measures of adherence above, there were five studies that used other adherence measures, ie, pill count,^{15,16} MAQ,³⁴ CRS,³⁴ mean drug plasma levels,³² and odds of missing a dose.³³ It was not possible to compare outcomes across these studies; however, the overall conclusions about dosing frequency and adherence per study are described below.

A prospective study in 52 patients with schizophrenia¹⁶ used pill count to assess adherence levels in patients on once-daily versus multiple daily dosing. When adherence was treated as a dichotomous variable using a threshold of 80%,

the adherence rate based on pill count was 76%. When adherence was treated as a continuous variable, the mean value for pill count was $85.45\% \pm 16.09\%$. Another prospective study in 26 patients with epilepsy¹⁵ also used pill count to assess adherence levels in patients on once-daily versus multiple daily dosing. Both studies^{15,16} found that adherence levels were higher in patients on less frequent dosing.

A survey study in 409 patients with schizophrenia³⁴ used MAQ to assess adherence levels in patients on once-daily versus multiple daily dosing. MAQ is a self-report that consists of four “yes/no” questions referring to the medication-taking behavior of the patient. The mean MAQ sum score was 2.97 ± 1.21 , and 47.2% of patients showed good adherence in the sense of their MAQ sum score equaling four. Contrary to all other studies, the adherence levels were lower in patients on less frequent dosing. In fact, the higher the daily dosing frequency, the better the adherence, as rated with the MAQ. The authors explained that one of the possible reasons is that patients benefit from strictly structured daily life. In this perspective, a daily routine of taking the medication at set time points might be helpful to enhance patient adherence by reducing the likelihood of forgetting to take the prescribed drugs. An alternative explanation might have been that attending psychiatrists prescribed high daily dose frequency only to their reliable (ie, adherent) patients.

A study in schizophrenia¹⁶ that compared adherence measures found that the capacity of clinicians to predict adherence was limited, with 42% of the subjects they identified as compliant being noncompliant based on MEMS results. Conversely, 44% of the group they identified as nonadherent was actually adherent according to MEMS data. Factors consistently associated with nonadherence included more severe symptomatology and increased dosing complexity, which is consistent with previous studies.

A retrospective study in epilepsy³² with 49 patients used mean drug plasma levels to assess adherence levels in patients on once-daily versus multiple daily dosing (twice, three and four times daily) and in patients on twice-daily versus multiple daily dosing. Adherence rates were higher in patients taking diphenylhydantoin twice daily versus multiple times daily (three and four times daily, $P < 0.001$). Paired *t*-statistics indicated that the statistical difference was significant in patients on diphenylhydantoin. A similar difference was found between the plasma levels for phenobarbital obtained between once-daily and multiple daily dosing (twice, three and four times daily, $P < 0.001$). Therefore, adherence levels were higher in patients on less frequent dosing.

Another study of 670 patients in epilepsy³³ used odds of missing a dose to assess adherence levels in patients on once-daily versus multiple daily dosing. Each increase in dose frequency increased the odds of missing a dose, which in turn led to an increase in the number of seizures. Results showed that each increase in dose frequency increased the likelihood of a seizure after a missed dose by 36%. The study found that only number of years taking seizure medication was significantly associated with the likelihood of missing a dose.

Discussion

Twelve studies on the impact of dosing frequency on adherence in epilepsy, schizophrenia, or depression were identified. Five studies each used a different measure of adherence (ie, pill count,^{15,16} MAQ,³⁴ CRS,³⁴ odds of missing a dose,³³ and mean drug plasma levels)³² so it was not possible to compare outcomes across these studies. Eight studies used common outcome measures, including MEMS,^{15–18} MPR,^{19–22} persistence^{19,21,22} or refill adherence.^{19,21,22} Half of these were small prospective studies of short duration using MEMS and half were large retrospective US database analyses of up to one year in duration using MPR with or without persistence and refill adherence measures. Four studies did not control for confounders in their analyses.^{15,18,31,32} Due to differences in study design, patient populations, and outcomes, it was not possible to pool results together with confidence. However, the findings from individual studies and from pooled results show that adherence is improved with once-daily dosing compared with more frequent daily dosing, regardless of the adherence measure used.

The results in depression studies enabled us to pool them together. When pooling the results together for the two depression studies that used persistence as a measure of adherence,^{19,22} an OR of 2.10 (95% CrL 1.86–2.37) was estimated. This means that the odds of patients on a once-daily regimen being adherent was more than twice the odds of being adherent for patients on twice-daily dosing. Our study confirmed these results also through pooling of results of depression studies^{19,22} when MPR was used as a measure of adherence. The pooled OR for these two depression studies^{19,22} was 1.89 (95% CrL 1.71–2.09), meaning that patients on once-daily dosing were 89% more adherent than patients on twice-daily dosing. The differences in adherence measures (ie, MEMS, change in MPR) across the schizophrenia and epilepsy studies alone were too large to allow pooling of results.

The major strength of this study is that, to the authors' knowledge, it is the first on this important topic. No other

systematic review was identified in schizophrenia, epilepsy, and depression on dosing frequency and adherence. A second strength of this systematic literature review is that its findings are in line with results from other therapeutic areas. A trend of better adherence with less frequent dosing was also found in review of chronic diseases with asymptomatic periods.³⁵ The review of chronic diseases with asymptomatic periods³⁵ could not perform statistical analyses of results or pool them together because of differences in study design, inclusion and exclusion criteria, different methods, and patient populations. Our review was able to pool data from some studies, although differences in populations, design, and measures of adherence made it difficult to combine all results identified.

A limitation of this review was that there were relatively few relevant studies identified, with small numbers of patients and short follow-up periods in some studies. Therefore, no clear conclusions about dosing frequency and adherence could be drawn in specific diseases (especially in epilepsy) or by duration of treatment. A second limitation was the lack of consensus on adherence measures and their interpretation across studies, which limits the scope for comparisons in general and the pooling of quantitative adherence data in particular. Moreover, although some adherence measures used, based on recorded bottle openings or prescription refill data, offer a more objective measure of adherence than self-reports, a bottle opening does not guarantee that the patient took the dose or the correct dose. Finally, adherence levels depend on study duration and the cutoff used for defining an adherent patient.

Further research that assesses the direct link between dosing regimen (controlling for confounding factors) and health outcomes (eg, relapse rates) through the mechanism of nonadherence would be valuable. Current studies assess either the link between dosing regimen and adherence, as in this review, or the relationship between nonadherence and health outcomes. Assessing the link between dosing frequency and hard endpoints in one study could be of interest to prescribers as well as health care policy-makers. Future studies that wish to allow for comparisons between studies, based on objective adherence measures, should consider using a common duration and cutoff definition.

All reviewed studies reached a similar conclusion, ie, that a simplified dosing regimen leads to improved adherence, regardless of the measure of outcome used, with the exception of the study by Meier et al.³⁴ In that study, MAQ was used as a measure of adherence which, in contrast with the other studies, reported that daily dose frequency was positively correlated with better patient adherence. One of the possible

explanations is that patients benefit from a strictly structured daily life.³⁴ An alternative explanation might be that attending psychiatrists prescribe high daily dose frequency only to their more reliable (ie, adherent) patients.³⁴

Nonadherence has a negative impact on patients' symptoms which can result in relapses and put an additional burden on health care resources. This costly problem that faces patients, health care providers and payers is increasingly recognized. While many factors are known to affect adherence, improving disease management by simplifying dosing regimens is one means to this end. This systematic review and meta-analysis suggests that there is an opportunity to improve outcomes for patients with chronic psychiatric diseases effectively by simplifying dosing regimens.

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