Dosing frequency and medication adherence in chronic disease

Coleman CI, Limone B, Sobieraj DM, Lee S, Roberts MS, Kaur R, Alam T

CRD summary
This review concluded that patients with chronic diseases appeared to adhere better to once-daily medication, than to more frequent dosing, and a more stringent definition of adherence showed a bigger effect. These conclusions may not be reliable, as there was no assessment of study quality and there were a number of limitations in the review methods.

Authors' objectives
To assess the effects of the recommended frequency of dose on medication adherence in patients with chronic diseases.

Searching
MEDLINE and EMBASE were searched for studies, in English, from 1986 (when the first electronic medication monitoring device was available) to December 2011. Search terms were reported. Reference lists of included studies and relevant systematic reviews were screened, as were bibliographies from an adherence monitor manufacturer (AARDEX Group)'s website.

Study selection
Randomised controlled trials (RCTs) and prospective observational studies were eligible for inclusion, if they evaluated oral medications (taken one to four times per day) in adults with at least one chronic disease, and had a follow-up of at least one month. The eligible studies had to electronically monitor the reported adherence. If patients were randomised to one or more interventions specifically designed to improve adherence, rather than monitor it, only the control arms were included. Studies of HIV, psychiatric illness, cancer, or treatment to prevent organ rejection, were excluded.

Over half of the included studies were of patients with cardiovascular diseases, the most common being hypertension, hyperlipidaemia, heart failure, stable angina, and anticoagulation. Other studies were of patients with neurologic conditions (epilepsy, migraine, or Parkinson's disease), type 2 diabetes mellitus, or asthma. The medications were condition-specific, such as warfarin for anticoagulation or beta-blockers for heart failure, or general, such as antihypertensive agents. Except for studies of epilepsy and asthma, where younger adults were enrolled, the mean or median age of patients ranged from 50 to 70 years. The proportion of men to women was approximately equal, in most studies. Three definitions were commonly used to measure adherence: taking adherence (the number of openings divided by the prescribed number of doses), regimen adherence (the percentage of days with the appropriate number of doses taken), and timing adherence (the percentage of doses taken within assigned intervals). Timing adherence was the most stringent definition. The included studies were published between 1987 and 2011. Nearly 40% of them were conducted in the USA; the rest were conducted in European countries, with six conducted in the UK.

Two reviewers independently assessed studies for inclusion, with any disagreement resolved by a third reviewer.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
The means and standard errors for adherence rates were extracted to calculate mean differences and 95% confidence intervals. Intervention arms, from included studies, were categorised into four dosing frequencies, ranging from one to four times per day. Study authors were contacted for additional data, where necessary.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
Weighted mean differences with 95% confidence intervals, for adherence rates, were calculated using random-effects meta-analyses. Meta-regression was used to evaluate the potential effects on the results, of a range of factors, including dosing frequency, disease state, study design, participants' awareness of electronic monitoring, and duration of monitoring.
Results of the review
Fifty-one studies were included in the review. There were 65 separate dosing-frequency arms for taking adherence, 76 for regimen adherence, and 47 for timing adherence. The treatment arms ranged in size from four to 501 patients. Eight studies were RCTs, 17 were post hoc observational analyses of randomised data, and 26 were observational studies. Follow-up ranged from 28 days to 365 days; 20% of studies had at least 168 days of follow-up.

With the least stringent definition of adherence (taking adherence), the unadjusted adherence ranged from 80.1% to 93.0%. With the most stringent definition (timing adherence), the unadjusted adherence ranged from 18.8% to 76.9%.

Meta-regression analyses showed that compared with once per day regimens, the adjusted weighted mean percentage adherence, for each regimen dosed more frequently than once per day, was significantly lower.

Compared with once per day, the difference in the adjusted weighted mean percentage, for taking adherence, was -6.7% for twice per day, -13.5% for three times per day, and -19.2% for four times per day. For regimen adherence, it was -13.1% for twice per day, -24.9% for three times per day, and -23.1% for four times per day. For timing adherence it was -26.7% for twice per day, -39.0% for three times per day, and -54.2% for four times per day.

Authors’ conclusions
Patients with chronic diseases appeared to adhere better to once-daily medication, than to more frequent dosing. A more stringent definition of adherence showed a bigger effect.

CRD commentary
The review question was clear and supported by appropriate inclusion criteria. Only two relevant databases were searched, so some relevant studies may have been missed. No specific attempts were made to find unpublished studies, leaving the potential for publication bias. The search was limited to studies in English, which may have introduced language bias. Steps were made to minimise reviewer error and bias in study selection, but it was unclear whether the same was true for data extraction. A formal quality assessment was not performed. The authors used meta-analyses to pool the study results, but they did not report the statistical heterogeneity. Pooling the results from studies with a variety of designs and populations may have not been appropriate.

The authors’ conclusions may not be reliable, as there was no assessment of study quality and there were a number of limitations in the review methods.

Implications of the review for practice and research
The authors did not state any implications for practice and research.

Funding
Supported by a grant from Janssen Scientific Affairs.

Bibliographic details

PubMedID
22971206

Original Paper URL
http://www.amcp.org/JMCP/2012/September/15591/1033.html

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Chronic Disease /drug therapy; Drug Administration Schedule; Humans; Medication Adherence; Monitoring, Ambulatory; Prescription Drugs /administration & dosage /therapeutic use
AccessionNumber
12012050469

Date bibliographic record published
17/01/2013

Date abstract record published
20/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.