

Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories

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ABSTRACT

Objective To describe characteristics of dosing history in patients prescribed a once a day antihypertensive medication.

Design Longitudinal database study.

Setting Clinical studies archived in database for 1989-2006.

Participants Patients who participated in the studies whose dosing histories were available through electronic monitoring.

Main outcome measures Persistence with prescribed antihypertensive treatment and execution of their once a day drug dosing regimens.

Results The database contained dosing histories of 4783 patients with hypertension. The data came from 21 phase IV clinical studies, with lengths ranging from 30 to 330 days and involving 43 different antihypertensive drugs, including angiotensin II receptor blockers (n=2088), calcium channel blockers (n=937), angiotensin converting enzyme inhibitors (n=665), β blockers (n=195), and diuretics (n=155). About half of the patients who were prescribed an antihypertensive drug had stopped taking it within one year. On any day, patients who were still engaged with the drug dosing regimen omitted about 10% of the scheduled doses: 42% of these omissions were of a single day's dose, whereas 43% were part of a sequence of several days (three or more days—that is, drug "holidays"). Almost half of the patients had at least one drug holiday a year. The likelihood that a patient would discontinue treatment early was inversely related to the quality of his or her daily execution of the dosing regimen.

Conclusions Early discontinuation of treatment and suboptimal daily adherence to execution of the prescribed regimens are the most common facets of poor adherence with once a day antihypertensive drug treatments. The shortfalls in drug exposure that these dosing errors create might be a common cause of low rates of blood pressure control and high variability in responses to prescribed antihypertensive drugs.

INTRODUCTION

Poor adherence with prescribed treatment continues to be one of the main causes of unsatisfactory control of blood pressure.¹⁻³ Although many studies have

examined the "adherence issue" over many years, the absence of a common taxonomy and the lack of reliable measurements of patients' exposure to prescribed pharmaceuticals have resulted in confusion, with "adherence rates" ranging from 35% to 97%.^{4,5}

One aspect of the problem is that traditional methods (pill counts, questionnaires, patients' diaries, measurements of drug concentration in plasma, etc) have repeatedly been shown to overestimate adherence.^{2,6,7} A reliable assessment of the prevalence of poor adherence can be inferred over long term follow-up from the timing of refills in large prescription databases,^{8,9} but refill audits do not show when dosing errors occurred. The same limitation applies to measurements of drug concentrations in plasma, which are also subject to bias created by white coat effects that increase adherence in the 24-48 hours before a scheduled visit to the clinic.¹⁰⁻¹³

A common error is the failure to distinguish between the two major components of a course of ambulatory pharmacotherapy: the quality of execution while the patient is engaged with his or her dosing regimen; and early discontinuation, known as "short persistence." The distinction between these two aspects of the patients' adherence to a prescribed regimen is crucial because the dynamics as well as the clinical and economic consequences of poor adherence and short persistence can differ markedly.

We characterised the most common dosing errors observed in a large group of patients with hypertension who were prescribed a once a day antihypertensive treatment.

METHODS

Study design and setting—We carried out a longitudinal study of patients' adherence to their once a day antihypertensive medications on the basis of dosing histories electronically compiled by a medication event monitor during phase IV clinical studies in 1989-2006. The monitors automatically record the date and time of each opening of the medication container.¹⁴

Patients—We included all patients who participated in clinical studies involving once a day antihypertensive drug treatments during 1989-2006

found in the Pharmionic Knowledge Centre database. Nearly all patients in the database were prescribed relatively recently introduced pharmaceuticals.

Definitions—We defined adherence as the extent to which patients' drug dosing histories conform to their corresponding prescribed drug dosing regimen. Adherence is broken into two main components¹⁵: persistence and execution. If on a given day the medication was not taken there can be two reasons: the patient had previously discontinued treatment (non-persistence) or the patient was still engaged with the dosing regimen but neglected to take a dose on that particular day (non-execution).

Statistical methods—We used Kaplan-Meier curves to display persistence over time. We identified any pattern of dosing histories that could jeopardise efficacy of treatment and investigated its prevalence in the population. We focused on omissions of dose on a single day and two consecutive days and drug holidays, defined as a sequence of at least three consecutive days without taking the drug. We estimated frequencies of single or sequential dose omissions within and between patients. Logistic models were used to test for potential changes in the daily probability of drug intake over time: days of the week and months of the year. Finally, we investigated the relation between execution and persistence by plotting and testing Kaplan-Meier estimates of persistence for different strata of execution.

RESULTS

The database contained dosing histories of 4783 patients. They came from 21 phase IV clinical studies, ranging in length between 30 and 330 days and involving 43 different antihypertensive drugs. The final dataset included data on 478 630 days of dosing history.

Figure 1 shows the results when we applied the definitions described in the methods. The persistence line represents the decline, since the start of treatment, in the proportion of patients who are still engaged with the dosing regimen. By the end of one year, almost half of the patients who were prescribed an antihypertensive medication have stopped taking the treatment, despite a dosing regimen indefinitely long. The initial abrupt small drop in the persistence curve represents the proportion of patients who never engaged with the dosing regimen (2% of the studied population). The persistence curve then decreases gradually but progressively over time. For example, at day 200, 35% of the patients have already stopped the treatment—that is, 65% persist with treatment. On, for example, the 200th day, among patients still engaged with the dosing regimen, 10% did not take their medication (non-execution). The percentage of the patients comprising the inception cohort who took their dose on day 200 is thus 58% (90%×65%), constituting a measure of overall shortfall in drug intake.

On each day of treatment, about 10% of scheduled doses were omitted. The breakdown of these omissions is as follows: 42% were omission of a single day's dose;

15% were omission of one or two consecutive days' doses, and 43% were one of a longer, multi-day sequence of omitted doses (three or more days). Almost 95% of the patients missed a single dose at least once a year. Half of the patients missed a single day's dose at a rate of one a month (12 a year); 48% of the patients took a drug holiday (>78 hours) at least once a year; and 13% had bi-monthly (six a year) drug holidays.

We identified periodic patterns in execution. There was a small but definite seasonal trend with a 2% reduction in execution between April and September ($P<0.001$). In a third of the patients we identified one or more days of the week on which errors occurred at exceptionally high rates: weekend doses were more likely to be missed than weekday doses (odds ratio 1.13, 95% confidence interval 1.12 to 1.15), but occasionally some patients had a particular weekday in which dosing errors were especially clustered. Finally, we classified patients as morning takers ($n=4149$), evening takers ($n=283$), and "variable" ($n=257$). Morning takers were more likely to take treatment correctly than evening takers (1.38, 1.36 to 1.41) and evening takers were more likely to take treatment correctly than variable takers (1.48, 1.45 to 1.52) (fig 2). Sunday morning was when morning takers missed most doses; Saturday evening was when evening takers missed most doses.

Stratifying estimates of persistence by the degree of execution showed that the better the execution, the longer the persistence. The likelihood that a patient would discontinue treatment early was related to the quality of his/her daily execution of the dosing regimen (hazard ratio 0.84 for 10% increase in execution; 95% confidence interval 0.81 to 0.87).

DISCUSSION

This retrospective analysis of dosing histories of patients prescribed once a day antihypertensive drugs showed that non-persistence is the leading problem with adherence: half of the patients stopped treatment within a year; 48% had at least one drug holiday a year

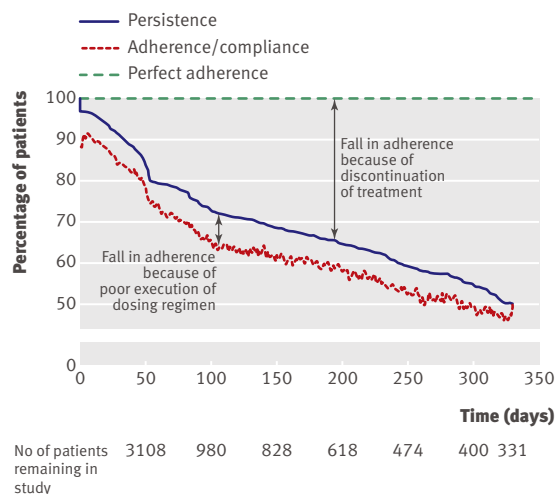


Fig 1 | Time course of adherence/compliance parameters (execution, persistence)

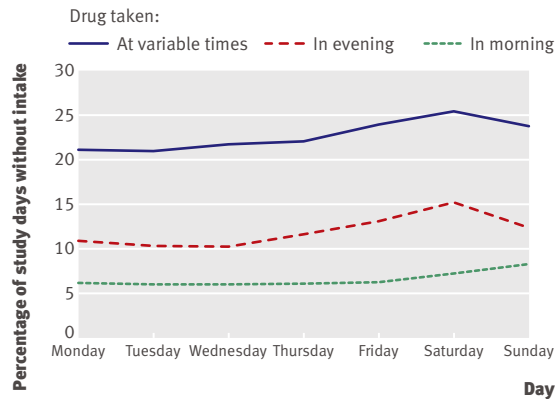


Fig 2 | Proportion of days without drug intake by day of week for each category of takers: morning, evening, or variable

and almost 95% missed at least a single dose a year; failure to take a dose was more common at weekends; the better a patient executed the drug regimen, the more likely he or she was to persist with the prescribed dosing regimen; morning dosing was more likely to be executed properly than evening dosing; and there was a small seasonal pattern of drug adherence.

Extent of the problem

According to our analysis, we can expect about half of the patients to stop treatment within one year, despite having been prescribed longer term treatment. The degree of persistence estimated from the database confirms the results obtained from the timing of refills in large prescription databases. In a population of 22 918 patients, Caro et al estimated the six month persistence to be 68%,⁸ hardly different from the present estimation of 66%.

Electronically compiled drug dosing history

Electronic monitoring of medication events—based on electronic detection of opening a container—is of course an indirect method of estimating when and how much drug is ingested. Results of investigations

comparing projected and periodically measured concentrations of drug in plasma have confirmed the validity of using medication event monitors,¹⁶⁻¹⁸ signifying that mismatches between medication events and actual dosing were rare.

Strengths and weaknesses

The studies included in this analysis are heterogeneous and represent an array of objectives, drugs used, and lengths of follow-up. They were, however, all phase IV studies of recently introduced antihypertensive agents, in general designed to show each agent's action in settings representative of expected clinical use in patients with uncomplicated hypertension.

Demographic characteristics were present for a minority of patients. The characteristics of these subsamples were consistent with the hypothesis that the studied population is probably representative of patients treated for uncomplicated hypertension.

Relevance of results

These results are clinically important in several ways. Firstly, they show the various dosing patterns that could be potential targets for the management of long term drug therapy. Patients who execute poorly need help in integrating their daily dosing into their routine, whereas patients who are at risk of imminent discontinuation need reinforcement and re-motivation to continue with the treatment. Our data suggest avoiding early discontinuation by re-motivation and improvement of the quality of regimen execution by helping patients to integrate their dosing into daily routines.^{19,20}

Whenever possible drugs should be taken in the morning, and patients and care givers should identify barriers to adherence during weekends and other leisure times. One aspect of this effort is the use, when possible, of antihypertensive drugs that have the ability to sustain full pharmacological action for one to two dosing cycles after a dose has been missed, and perhaps longer.

Lastly, the low persistence and the frequency of missed doses in these studies questions the validity of drug trials in which neither persistence nor execution are measured and taken into account.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Poor adherence to antihypertensive treatment is a major therapeutic challenge and contributes to the lack of adequate control in more than two thirds of patients with hypertension

Although “adherence” seems a simple construct, often reduced to a percentage of prescribed doses taken, electronically compiled dosing histories reveal variably long intervals between doses and variably short durations of treatment

WHAT THIS STUDY ADDS

The principal modes of non-adherence are quitting treatment early, and, before treatment ends, suboptimal execution of the once a day dosing regimen, with intervals between doses of three or more days

About half of patients quit treatment within the first year; they made many more errors in execution of the dosing regimen than those who continued treatment

Patients who omit sequential doses are at highest risk of quitting early and should be targeted and proactively re-motivated to continue treatment

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Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis

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ABSTRACT

Objective To determine the accuracy of using systolic and diastolic blood pressure, mean arterial pressure, and increase of blood pressure to predict pre-eclampsia.

Design Systematic review with meta-analysis of data on test accuracy.

Data sources Medline, Embase, Cochrane Library, Medion, checking reference lists of included articles and reviews, contact with authors.

Review methods Without language restrictions, two reviewers independently selected the articles in which the accuracy of blood pressure measurement during pregnancy was evaluated to predict pre-eclampsia. Data were extracted on study characteristics, quality, and results to construct 2×2 tables. Summary receiver operating characteristic curves and likelihood ratios were generated for the various levels and their thresholds.

Results 34 studies, testing 60 599 women (3341 cases of pre-eclampsia), were included. In women at low risk for pre-eclampsia, the areas under the summary receiver operating characteristic curves for blood pressure measurement in the second trimester were 0.68 (95% confidence interval 0.64 to 0.72) for systolic blood pressure, 0.66 (0.59 to 0.72) for diastolic blood pressure, and 0.76 (0.70 to 0.82) for mean arterial pressure. Findings for the first trimester showed a similar pattern. Second trimester mean arterial pressure of 90 mm Hg or more showed a positive likelihood ratio of 3.5 (95% confidence interval 2.0 to 5.0) and a negative likelihood ratio of 0.46 (0.16 to 0.75). In women deemed to be at

high risk, a diastolic blood pressure of 75 mm Hg or more at 13 to 20 weeks' gestation best predicted pre-eclampsia: positive likelihood ratio 2.8 (1.8 to 3.6), negative likelihood ratio 0.39 (0.18 to 0.71). Additional subgroup analyses did not show improved predictive accuracy.

Conclusion When blood pressure is measured in the first or second trimester of pregnancy, the mean arterial pressure is a better predictor for pre-eclampsia than systolic blood pressure, diastolic blood pressure, or an increase of blood pressure.

INTRODUCTION

Blood pressure measurement is routinely used in antenatal care to detect or predict hypertensive disease.¹ The results from studies on the predictive accuracy of such measurements have conflicted and it is therefore uncertain whether blood pressure measurement should be used routinely as a predictive test or used only to diagnose suspected hypertensive disorders in pregnancy. We carried out a systematic review to investigate the accuracy of blood pressure measurement for prediction of pre-eclampsia in pregnant women.

METHODS

We included studies that reported on any technique to measure blood pressure in pregnant women in any healthcare setting and of any level of risk for pre-eclampsia (see bmj.com for search strategy). We