A review of studies of adherence with antihypertensive drugs using prescription databases

Nicola Fitz-Simon
Kathleen Bennett
John Feely

Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland

Abstract: Poor adherence with antihypertensive therapies is a major factor in the low rates of blood pressure control among people with hypertension. Patient adherence is influenced by a large number of interacting factors but their exact impact is not well understood, partly because it is difficult to measure adherence. Longitudinal prescription data can be used as a measure of drug supply and are particularly useful to identify interruptions and changes of treatment. Obtaining a medicine does not ensure its use; however, it has been established that continuous collection of prescription medications is a useful marker of adherence. We found 20 studies published in the last 10 years that used large prescription databases to investigate adherence with antihypertensive therapies. These were assessed in terms of patient selection, the definition of the adherence outcome(s), and statistical modeling. There was large variation between studies, limiting their comparability. Particular methodological problems included: the failure to identify an inception cohort, which ensures baseline comparability, in four studies; the exclusion of patients who could not be followed up, which results in a selection bias, in 17 studies; failure to validate outcome definitions; and failure to model the discrete-time structure of the data in all the studies we examined. Although the data give repeated measurements on patients, none of the studies attempted to model patient-level variability. Studies of such observational data have inherent limitations, but their potential has not been fully realized in the modeling of adherence with antihypertensive drugs. Many of the studies we reviewed found high rates of nonadherence to antihypertensive therapies despite differences in populations and methods used. Adherence rates from one database ranged from 34% to 78% at 1 year. Some studies found women had better adherence than men, while others found the reverse. Novel approaches to analyzing data from such databases are required to use the information available appropriately and avoid the problems of bias.

Keywords: patient adherence, antihypertensives, prescription databases

Introduction

Recent guidelines emphasize the importance of blood pressure control to reduce cardiovascular morbidity and mortality (Guidelines Committee 2003). However, control of blood pressure among hypertensives remains low – at approximately 13% in the UK (Health Survey for England 2002). One of the reasons for this is poor adherence with therapeutic regimens; Flack et al (1996) have previously documented the relationship between poor adherence and lack of blood pressure control. DiMatteo et al (2002) found a difference in blood pressure of 30% (95% confidence interval 12%, 46%) between hypertensive patients with high and low adherence.

The WHO definition of adherence is "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO 2003, p 3).

Correspondence: Nicola Fitz-Simon
Department of Pharmacology and Therapeutics, Trinity Centre for Health Sciences, St James's Hospital, Dublin 8, Ireland
Tel +353 1 6081408
Fax +353 1 4539 033
Email afitzsim@tcd.ie

A variety of terms are used for outcome measures in quantitative studies of adherence; here we use the WHO definition for adherence and terms used in individual studies according to their own definitions.

While collection of a prescription does not ensure its use, assessment of adherence with antihypertensive regimens using prescription data has been validated by comparison with electronic monitoring (MEMS) (Choo et al 1999) and other measures of compliance and drug presence or effect (Steiner and Prochazka 1997). Steiner and Prochazka, in their assessment of refill compliance using pharmacy claims data concluded that in large populations, this type of data "can provide otherwise unobtainable information about the pattern and timing of drug exposure, and the determinants and consequences of adherence" (Steiner and Prochazka 1997, p 105). They also found that the acquisition of drug oversupplies was rare.

Prescription claims data are especially useful for identification of nonadherence in the sense of discontinuation or changes in treatment. For adequate determination of drug exposure patterns, it is necessary that all prescriptions received by the patient during the observation period are recorded in the database; that is, patients do not collect prescriptions from some other source, and the recording process is reliable.

Methods of assessment of adherence using prescription refill data tend to be nonsystematic owing to use of different definitions, and results are often not directly comparable. The aim of this study is to examine the approaches to investigating adherence with antihypertensive medications using prescription databases.

Search criteria for inclusion

We made a comprehensive search for articles published in the last 10 years (1995–2004) that used prescription claims data to estimate adherence with antihypertensive therapies. This included searches of PubMed, CINAHL, and individual journals. The criteria for selection were the combination of terms for adherence with a term indicating hypertension and the term "prescription". Relevant references were identified from the bibliographies of selected articles.

We assessed articles in terms of information available in the database, selection of patients and therapies – particularly the validity of patient exclusions – definition of the outcome measures used to assess adherence, and statistical methods used. We compared the methods and results between certain studies included in the review.

Based on the selection criteria described above, we found 20 relevant articles published between 1995 and 2004 that examined adherence to antihypertensive therapies. All were based on European or North American prescription databases that allowed the construction of longitudinal patient prescription histories. The majority of these studies were based on US populations, where databases included Medicaid and Medicare claims (Monane et al 1997; Rizzo and Simons 1997), the US Department of Defense United Services Personnel Drug Program (USPDP) (Okano et al 1997), Veterans' Health Administration (VHA) databases (Ren et al 2002; Wang et el 2002), and pharmacy benefits managers (PBM) databases (Bloom 1998; Benson et al 2000; Dezii 2000; Conlin et al 2001; Wogen et al 2003; Taylor and Shoheiber 2003). The Canadian studies were based on the Saskatchewan Health database (Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Bourgalt et al 2001; Marentette et al 2002). The European studies included a UK study based on the Mediplus automated primary care database (Jones et al 1995), an Italian prescription database for the Local Health Unit in Ravenna (Degli Esposti E et al 2002; Degli Esposti L et al 2002; Degli Esposti et al 2004), and the Mediplus data of IMS Health, an insurance system covering patients in France, Germany, and the UK (Hasford et al 2002).

Some of the prescription databases were specific to populations with characteristics known to influence adherence; for instance, insurance coverage, where patients paying for their treatment may be more likely to adhere to therapy. Therefore, it may not be appropriate to extrapolate the conclusions of these studies to populations that do not share these traits.

Table 1 summarizes the information available from each study. Some databases included information on diagnoses or could be linked by patient to diagnosis codes (which might be available only in the event of a hospital discharge). Many of the databases did not include information on diagnoses. All databases included a unique patient identifier, demographic information (minimally age and sex of the patient), and information on all prescriptions received, including date of prescription and type and quantity of the drug received. None included information on what was actually prescribed as opposed to what was claimed. Two studies included patient questionnaires or interviews.

Patient selection criteria for individual studies

Table 1 gives the characteristics of the study populations considered in each study identified as described above.

Table 1 Characteristics of study populations

Reference	Nr of subjects	Follow-up	Diagnosis	Age (y)	Antihypertensive drugs	New	Observation time	Other selection
Jones et al (1995), UK Mediplus	10 222	6 mo	ICD-9 401-405	>40	ACE, BB, CCB, diuretic	4 mo that AHT	Visits for 6-mo observation period	All new courses AHT
Monane et al (1997), New Jersey Medicaid Medicare	8643	1 y	Hospital discharge only	65–99, mean 75.6 (SD 8.1)	Any AHT ≥ 1-mo supply	12 mo any AHT; new only	Active use; at least 1 claim each 4 mo	Hospital, nursing home etc patients excluded
Rizzo and Simons (1997) Pennsylvania Medicaid	7211	1 y	ICD-9 401, 401.1, 401.9	Mean 59.4 (SD 13.9)	ACE, BB, CCB, diuretic Monotherapy ≥ 1-mo supply	Not identified	Continuous eligibility	Nursing home excluded random sample selected
Okano et al (1997), US Dept Defense USPDP	771	1 y	No	20–49	ACE, CCB	6 mo selected AHT; new only	Continuous enrolment claims at start and end	771/5947 enrolled continuously
Bloom (1998) Merck-Medco managed care	21 723	1 y	No	35–71, mean 56	ACE, BB, CCB, thiazide, AT2 monotherapy	12 mo any AHT; new only	Not stated; dropouts considered to have stopped?	Exclude nitrates, antiarrhythmics, digoxin, warfarin, loop diuretics, and migraine medicines
Caro, Salas, et al (1999) Saskatchewan Health	74 181	5 y unless censored	ICD-9 401, 401.1, 401.9	>40, median 65	ACE, BB, CCB, diuretic, combination other (All 56 AHTs in Saskatchewan formulary)	10 mo any AHT; new vs established	Patients observed minimum 1 y, 5410 exclusions	Exclude other CVD, hepatic and renal disease, and pregnant women
Caro, Speckman, et al (1999) Saskatchewan Health	22 918	5 y unless censored	ICD-9 401, 401.1, 401.9	>40, median 63	ACE, BB, CCB, diuretic monotherapy	10 mo any AHT; new only	Censoring after 6-mo observation	Exclude other CVD, hepatic and renal disease, and pregnant women
Benson et al (2000) US HMO	7490	1 y	No	>30	Amlodipine, atenolol, HCTZ/triamterene, lisinopril, losartan, nifedipine, quinapril	90 days any AHT; new only	Continuous eligibility	Discontinue in first year; min 30 days therapy; max 1200 per drug
Dezii (2000) US PBM	3942	1 y	No	Not given	Lisinopril or enalapril + HCTZ Single tablet or 2 separate tablets	6 mo any AHT; new only	Continuous eligibility; some claim at 1 y	None
Bourgalt et al (2001) Saskatchewan Health	19 501	5 y unless censored	Hospital discharge diagnosis only	40–79, mean 60	ACE, BB, CCB monotherapy or combination	12 mo any AHT including diuretics, α-blockers, etc; new only	Included	Exclude CVD (ICD-9 402, 404, 410–416, 420–429, 745.4–746.9) and anticoagulants, loop diuretics, cardiac thyroid and migraine medicines
Conlin et al (2001) Merck-Medco managed care	15 175	4 y, same cohort as Bloom	No	35–71, mean 56	ACE, BB, CCB, diuretic, AT2 monotherapy	12 mo any AHT; new only	Continuous eligibility, 6548 excluded from Bloom cohort	Exclude nitrates, antiarrhythmics, digoxin, warfarin, loop diuretics, and migraine medicines

Table 1 *continued*

Reference	Nr of subjects	Follow-up	Diagnosis	Age (y)	Antihypertensive drugs	New	Observation time	Other selection
Ren et al (2002) Boston Veterans' Health	1292 (59% response)	2 y	Not stated	Mean 65.2 (SD 10.3)	Any AHT	Not identified	Observed 2 y complete	None
Degli Esposti E et al (2002) Ravenna LHU	7312	3 y	No (hospital discharge only)	>20	ACE (C09A), BB (C07), CCB (C08), diuretic (C03), AT2 (C09C); monotherapy	12 mo any AHT; new only	Leave/die excluded 478	Exclude if <7 days treatment
Marentette et al (2002) Saskatchewan Health	46 458	5 y	ICD-9 401-405	1–95, mean 61	ACE, BB, CCB, AT2, diuretic; initial class only; diuretic + AHT classified with other AHT. Mixed classes ≥1 class	12 mo any AHT; new only	4571 (9%) patients excluded as not observed entire period	Exclude patients receiving α-blockers, α-agonists, and vasodilators
Wang et al (2002), US HMO and Veterans' Health	496 (50% response)	1 y	HT in previous year	>40	Any AHT	180 days any AHT; new only	Continuous enrolment	Random sample eligible patients sent questionnaire
Hasford et al (2002), IMS Health Mediplus	2416	1 y	New HT	Mean 61 (SD 12.7)	ACE, BB, CCB, diuretic, AT2 monotherapy	New -exclude if HT diagnosis previous year	Lost to follow-up classed discontinued	Patients matched to irbesartan group
Degli Esposti L et al (2002) Ravenna LHU	16 783	1 y	No	>20, mean 56.1 (SD 18.3)	ACE (C09A), BB (C07), CCB (C08), diuretic (C03), AT2 (C09C); monotherapy	12 mo any AHT; new only	Leave/die excluded (660)	None
Wogen et al (2003) US PBM	142 945	1 y	No	Mean 63.1 (SD 14.0)	Valsartan, amlodipine, lisinopril	12 mo that class; new only	Continuous eligibility	None
Taylor and Shoheiber (2003) US PBM	5732	1 y	Yes	18–64	Amlodipine/ benazepril or ACE + CCB	Not identified	Continuous eligibility	None
Degli Esposti et al (2004) Ravenna LHU	14 062	1 y	No	>20	ACE, BB, CCB, diuretic, AT2 monotherapy	12 mo any AHT; new only	Leave/die excluded (817)	None

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; BB, β-blocker; CCB, calcium channel blocker; AT2, angiotensin-II antagonist; AHT, antihypertensive; HCTZ, hydrochlorothiazide; ICD, International Classification of Diseases; CVD, cardiovascular disease; HT, hypertension; min, minimum; max, maximum; mo, month; y, year.

Diagnostic data

Where diagnosis data were available, patients were included in the study cohort based on this and prescription of selected drugs. Diagnoses allowed varied between studies: in three studies patients with the International Classification of Diseases – 9th Revision (ICD-9) codes 401, 401.1, and 401.9, referring to essential hypertension and benign and unspecified hypertension, were included (Rizzo and Simons 1997; Caro, Salas, et al 1999; Caro, Speckman, et al 1999), while elsewhere patients with ICD-9 codes 401–405 were

chosen (Jones et al 1995; Marentette et al 2002), or it was merely stated that patients had a diagnosis of hypertension (Hasford et al 2002; Wang et al 2002).

Where diagnosis data were not available, patients were selected on the basis of prescription of selected drugs, with possible exclusions of patients based on other prescriptions. The chosen antihypertensive drugs varied according to the study. They included a selection from angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, diuretics, and angiotensin-II antagonists,

some studies choosing particular drugs and others including all drugs in each class.

In some instances patients with diagnoses indicating cardiovascular and other comorbidities were excluded (Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Bourgalt et al 2001) and in others this information was used to construct covariates to be included in the predictive models for adherence (Rizzo and Simons 1997; Degli Esposti E et al 2002; Degli Esposti L et al 2002; Degli Esposti et al 2004). Similarly, the use of other drugs that could indicate certain conditions such as angina and heart failure was used as a basis for exclusion from the cohort (Bloom 1998; Bourgalt et al 2001; Conlin et al 2001) or included as covariates (Degli Esposti E et al 2002; Degli Esposti L et al 2002; Wogen et al 2003; Degli Esposti et al 2004).

Monotherapy and combinations

Eight studies included only patients initiating antihypertensive monotherapy. In the other studies patients could be receiving prescriptions for single therapies or combinations. In some studies combinations of antihypertensives were treated as a separate drug class (Bourgalt et al 2001; Marentette et al 2002), while in others the prescription of other antihypertensives was controlled for by including appropriate covariates in the model for adherence (Rizzo and Simons 1997; Wogen et al 2003). Two studies compared adherence to combinations in single-tablet or separate-tablet forms (Dezii 2000; Taylor and Shoheiber 2003). Some studies appear to have ignored or not specified how they handled combinations of antihypertensive treatments in their analyses.

New users of antihypertensives

Most studies identified patients who were new users of antihypertensive drugs; three did not (Rizzo and Simons 1997; Ren et al 2002; Taylor and Shoheiber 2003). Identification of new patients allows baseline and subsequent comparability: duration of therapy is known to have a major influence on adherence, with those on therapy longer being less likely to discontinue (Sackett 1976). Based on the known reduction of the risk of discontinuation as duration of therapy increases, most studies excluded established users of antihypertensives. These patients' total time on therapy is unknown and therefore the effect of therapeutic duration on the risk of stopping therapy cannot be assessed. New users were determined in various ways, from diagnosis date (one study; Hasford et al 2002) or by evidence of a period without therapy previous to the inception date. The length

of this period ranged from 3 to 12 months; however, there was usually no attempt to justify this choice. A study based on the UK General Practice Research Database (UKGPRD) concluded that a 4-month period without prescriptions was not sufficiently long to identify new users of antihypertensive drugs and that a 12-month period would be more appropriate (Suarez et al 2000). This finding is not necessarily applicable to other databases, but it is possible that the studies choosing relatively short run-in periods may include a substantial number of patients who are not new to antihypertensive therapy. In the studies reviewed, patients were variously considered new to therapy if they had received no antihypertensive prescriptions, no prescriptions for drugs in the same class, or no prescriptions of the particular drug during this period. Patients who have previously been prescribed a different antihypertensive are not new to therapy; they have been prescribed antihypertensives for an unknown duration. Changing to a new type of therapy does not make them new users, but three studies included them as such (Jones et al 1995; Okano et al 1997; Wogen et al 2003). In principle, the ideal inception cohort consists of recently diagnosed patients who are new to therapy, and given that 12 months without therapy is a sufficient period for identification of these, it appears that only half these studies chose satisfactory inception cohorts.

Follow-up

To determine adherence, it is necessary that all prescriptions received during the period of observation are recorded in the database. This requires that patients receive all their prescriptions under the scheme and that all claims are properly recorded. Many studies required continuous eligibility, excluding patients who died, moved away, or otherwise became ineligible for the particular scheme. For instance, three-quarters of initially identified patients from the US Department of Defense cohort (Okano et al 1997) were excluded because there were insufficient follow-up data. However, these patients could be included if censoring techniques had been used, thus allowing patients who are observed for varying lengths of time from the date of inception to be included in the study cohort (Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Bourgalt et al 2001).

Other variables

Many studies excluded patients on the basis of age; age groups selected ranged from a relatively young cohort aged 20–49 years (Okano et al 1997) to elderly patients aged 65–99 years (Monane et al 1997).

As all the factors listed above that were used to select the study cohorts – particular antihypertensive, co-prescriptions, number of drugs, duration of use, and age – may be associated with adherence to antihypertensive therapy (WHO 2003), it is necessary to interpret the results of a particular study in terms of patient selection.

Outcome definitions

Table 2 gives a summary of outcome definitions and rates estimated for each study. There was no consistent agreement either in the terms used for outcomes or in their definitions. Outcomes were measured as a dichotomous variable (eg, compliant versus noncompliant) or as a continuous variable (eg, proportion of days covered expressed as a percentage). Outcomes might be measured at one point in time, at several selected time points, or continuously.

Persistence

One type of outcome measure included variations on the idea of still taking therapy after a period of time (for instance, 1 year). In some cases this type of measure focused on use of the initial therapy, sometimes on use of the initial class, and sometimes on use of any antihypertensive therapy. The term usually used for this type of outcome was "persistent", although "continuation" was also used.

In two studies patients were defined as persistent if they refilled their initial prescriptions on or within 3 months of the 1-year anniversary of the starting date (Bloom 1998; Conlin et al 2001); similarly "continuous treatment" required a duration of over 273 days during a year of observation (Degli Esposti L et al 2002). Elsewhere patients were considered persistent if their final prescription covered the period until the end of observation (Caro, Salas, et al 1999; Caro, Speckman, et al 1999). Yet another definition of persistence required that the patient did not miss any three scheduled monthly refills during the course of a year (Dezii 2000).

Compliance

The term "compliance" was usually used for outcome measures based on the proportion of days covered (PDC); that is, the number of days the patient had a prescription available divided by the time observed. As in the approach described above, this might include the initial therapy only, the initial class, or any antihypertensive, depending on the study. In some studies patients were defined to be compliant if their PDC was greater than 80%, while in other studies compliance was treated as a continuous measure. The terms "adherence" and "continuous use" were also used for this type of measure. The term "persistent" was also used for patients collecting a certain proportion of prescriptions during the time observed. The use of the same terms in different approaches highlights the inconsistencies in the definitions of terms used in the literature.

Several studies considered patients to be compliant if the prescriptions they received covered over 80% of the duration of observation (Monane et al 1997; Okano et al 1997; Rizzo and Simons 1997). It has been observed that patients receiving at least 80% of their medication are more likely to achieve blood pressure control in both active treatment and placebo groups (Black et al 1987). But this does not make allowance for differences between antihypertensive drugs or differences in patients' responses to therapy. Some studies used the percentage of days with drugs available as a continuous outcome variable (Rizzo and Simons 1997; Taylor and Shoheiber 2003; Wogen et al 2003).

Discontinuation

Discontinuation was generally defined as a gap in treatment exceeding some specified time ranging from 30 to 90 days. There were no attempts to validate the choice of duration of the period without therapy. Suarez et al (2000), in their study of the UKGPRD, found that 4 months was an insufficient period for identification of new users of antihypertensive therapies; that is, they found that there were a large number of patients who, although failing to collect their prescriptions for 4 months, returned to some form of antihypertensive therapy. If this finding holds true for other populations, it appears that many discontinuations may be more properly regarded as breaks in therapy. It is important to define discontinuation in the context of the population studied. It is also important to follow patients throughout the period of observation, rather than regarding such gaps in therapy as final.

Duration of prescription availability was calculated as time from the initial prescription until the date of discontinuation. Several studies classified patients as continuers, discontinuers, or switchers and calculated rates for each outcome (Jones et al 1995; Dezii 2000; Bourgalt et al 2001; Degli Esposti E et al 2002; Degli Esposti L et al 2002).

Table 2 Outcome definitions and rates

Reference	Outcomes	Continuing rates	Switching rates
Jones et al (1995)	Continuation = still taking initial therapy (class); not continuing if gap > 60 days Switch = stop initial therapy and prescribed AHT from different class	6 mo (calculated monthly); diuretic 41%, BB 49%, CCB 41%, ACE 45%	6 mo: diuretic 49%, BB 43%, CCB 52%, ACE 48%
Monane et al (1997)	Compliant = PDC > 80% any AHT Switches included as compliant	Calculated at 1 y; 20% patients compliant	
Rizzo and Simons (1997)	Compliance = PDC averaged over all AHT classes Switches included as compliant	Calculated at 1 y: overall estimates; diuretic 5%, BB 29%, CCB 35%, ACE 35%	
Okano et al (1997)	Continuous use = PDC > 80% on any AHT Switches included as continuous use; tabulated for continuous users at 1 y	At 1 y: continuous use any AHT: ACE 55.5%, CCB 49.4%; initial therapy only (including dose changes) ACE 35.4%, CCB 26.6%	1 y switches/additions of therapy; ACE 20.1%, CCB 22.8%
Bloom (1998)	Persistent = refill initial prescription at 12 (+ 3) mo Switch is change of AHT class	Calculated at 1 y; diuretic 38%, BB 43%, CCB 50%, ACE 58%, AT2 64%	1 y; diuretic 6%, BB 7%, CCB 9%, ACE 9%, AT2 7%
Caro, Salas, et al (1999)	Persistent (+ cumulative rates) = last prescribed AHT covers period until end of observation, allowing for previous accumulation; switches included as persistent	1 y; established 97%, new 78%	
Caro, Speckman, et al (1999)	Persistent (+ cumulative rates) = last prescribed AHT covers period until end of observation, allowing for previous accumulation; switches included as persistent	6 mo; diuretic 80%, BB 85%, CCB 86%, ACE 89%	
Benson et al (2000)	Duration = date last prescription + days covered by this – start date. Discontinued if initial AHT not available > 30 days and no AHT within 90 days of end	Median duration: 90 days all drugs except HCTZ comb. 80 days. Note: only patients who discontinued AHTs included	
Dezii (2000)	Persistent (monthly) = initial AHT without missing > 3 prescriptions in year observed Not persistent if failing to renew 3 prescriptions during year	At 1 y (calculated monthly); lisinopril /HCTZ 1 tab 68.7%, 2 tabs 57.8%	
Bourgalt et al (2001)	Time to first modification = any change of initial therapy (drug titration allowed) Switch = change therapy (class) and stop initial AHT; maximum gap 90 days	1 y no modification 33.8%; 5 y no modification 11.5%; BB 7.9%, CCB 9.3%, ACE 13.1%, combination 22.3%	1st modification: addition 20.1%, switch 14.3%, interruption (gap > 90 days) 31.5%, discontinue 22.6%
Conlin et al (2001)	Persistent = refill initial AHT at 12, 24, 36, 48 (+ 3) mo Switch = no initial AHT and change AHT class in follow-up intervals	At 1 y (calculated yearly); diuretic 20.8%, BB 45.6%, CCB 54.1%, ACE 60.7%, AT2 67.4%	1 y; diuretic 18.8%, BB 6.4%, CCB 9.8%, ACE 9.6%, AT2 8.0%
Ren et al (2002)	Compliance rates = PDC any AHT excluding last prescription Compliant = PDC > 80% not including last prescription	At 2 y; compliant 72.8%	
Degli Esposti E et al (2002)	Persistence = duration first–last prescription any AHT; continuing if > 1 AHT each year Switches include continuers	3 y; 57.9% continue	Restart 7.6%; ≥ 2 AHTs 1st and 3rd year and < 2 AHTs 2nd year
Marentette et al (2002)	Persistence = prescription from initial class only within previous 90 days at 4 time points Switches included in "mixed" class	Calculated at days 180, 360, 540, 720; 360 days overall 63.8%; 180 days diuretic 52.0%, BB 67.2%, CCB 69.8%, ACE 75.1%, AT2 87.8%	180 days; mixed 79.7%

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Table 2 *continued*

Reference	Outcomes	Continuing rates	Switching rates
Wang et al (2002)	Compliance = PDC any AHT tertiles (50%, 80%) Switches included as compliant	Calculated at 1 y; PDC > 80% in 29% of patients	
Hasford et al (2002)	Persistence = initially prescribed monotherapy; discontinue = gap > 30 days Switch = any change from initial monotherapy Duration on initially prescribed monotherapy (until switch/discontinue/end observation)	1 y overall 46.8%; diuretic 34.4%, BB 49.7%, CCB 43.6%, ACE 42.0%, other AT2 51.3%, irbesartan 60.8%	1 y; add 23.8%, change 12.9%
Degli Esposti L et al (2002)	Persistence = continue with initial therapy after 9 mo (continuers/switchers) Duration any AHT time covered first–last prescription	1 y overall 26.9%; diuretic 23.1%, BB 30.9%, CCB 23.7%, ACE 30.7%, AT2 33.4%	1 y overall 8.2%; diuretic 7.1%, BB 6.7%, CCB 7.6%, ACE 9.4%, AT2 24.6%
Wogen et al (2003)	Persistence = remain on initial AHT no gaps > 60 days Switches not analyzed. Duration = last prescription date – first prescription date (initial AHT)	1 y overall 54%; valsartan 63%, amlodipine 53%, lisinopril 50%	
Taylor and Shoheiber (2003)	Adherence = PDC excluding last prescription 2 tablets: time is first prescription second drug – last prescription last drug (ie, sequential/combined)	Calculated at last prescription observed: combination 80.8%, ACE + CCB 73.2%	
Degli Esposti et al (2004)	Persistence = continue with initial therapy after 9 mo (continuers/switchers) Duration any AHT time covered first–last prescription	1 y overall 30.9%; diuretic 25.9%, BB 36.9%, CCB 26.9%, ACE 32.2%, AT2 41.7%	1 y overall 8.8%; diuretic 7.3%, BB 6.5%, CCB 8.6%, ACE 10.6%, AT2 13.2%

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; BB, β-blocker; CCB, calcium channel blocker; AT2, angiotensin-II antagonist; AHT, antihypertensive; HCTZ, hydrochlorothiazide; PDC, proportion of days covered; mo, month; y, year.

Change of therapy

Some studies considered switches or changes of regimen as continuation of therapy (Monane et al 1997; Okano et al 1997; Rizzo and Simons 1997; Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Degli Esposti E et al 2002; Ren et al 2002; Wang et al 2002), whereas others classified this as discontinuation of the initial therapy. The studies that focused on continuation with the initial therapy mostly ignored additional drugs (Jones et all 1995; Bloom 1998; Benson et al 2000; Dezii 2000; Conlin et al 2001; Degli Esposti L et al 2002; Wogen et al 2003) but in some instances classified these as modification of therapy (Bourgalt et al 2001; Hasford et al 2002). To get a clearer picture of prescription patterns, information on prescriptions of antihypertensives other than the therapy initially prescribed should be included in the analysis. This information should include time and type of therapy. Analysis of such information requires the use of an appropriate statistical model.

The broad definition of adherence as proposed by the WHO allows flexibility in the definition of quantitative measures. This is useful, as it encompasses the many aspects of adherence. But because there is no standard quantitative definition, care must be taken in the interpretation of studies that attempt quantitative assessment of adherence. A further complication is the use of the same terms to mean different things. Quantitative studies of adherence should be interpreted in the light of the definitions they use and their justification of these definitions.

Outcome rates and analyses

Table 3 gives details of the results on adherence rates according to individual study definitions and includes associations with other variables.

Models used

The earlier studies limited their measurement of outcomes to a single point in time and in some cases no modeling was attempted, the focus being on the level of adherence as defined by the particular study at this point in time. Several studies examined the significance of chosen covariates using logistic regression (Hosmer and Lemeshow 2000) typically to predict good adherence or persistence at 1 year (Monane et al 1997; Bloom 1998; Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Wogen et al 2003). Good compliance at 1 year was predicted using age, sex, type of

Table 3 Summary of results from the studies

Reference	Survival analysis	Other analyses	Control	Significant	Nonsignificant	Comments
Jones et al (1995)		ANOVA Compare continuers vs switch/discontinue		Continuers: nr of GP visits inc, nr of AHT prescriptions dec (significance levels not given)		Frequency of continuation decreased with duration
Monane et al (1997)		Logistic for good compliance at 1 y	Age (3 groups), sex, race, start year	OR (95% CI) Thiazide 1.0, BB 1.4 (1.2, 1.7), CCB 1.7 (1.5, 2.1), ACE 1.9 (1.6, 2.1), CHF/CAD 1.2, >8 GP visits 2.2, >8 other medicines 0.8, redeem at >1 pharmacy 0.4	Thiazide dose	Analysis repeated for patients with >1 prescription and with CHF/CAD – same
Rizzo and Simons (1997)		OLS for 1 y compliance		Duration dec, BB duration inc, CCB duration inc, ACE duration inc, age inc, white inc, medical resources inc, CHF inc	Sex, asthma, COPD, diabetes, renal failure, angina, LVH, AMI, PAD, TIA	Significance level 0.01 Also OLS regression for costs
Okano et al (1997)		None				Tables for rates of compliance only
Bloom (1998)		Logistic for persistence at 12 mo		OR (95% CI) Thiazide 0.36 (0.30, 0.43), BB 0.56 (0.47, 0.68), CCB 0.62 (0.51, 0.74), ACE 0.81 (0.68, 0.97), AT2 1.00, age >65 y 1.00, age 40–65 y 0.79, age <40 y 0.32; >1 dose/day 1.40		Sex – OR is 1.08 (1.02–1.15); clinically uncertain and don't specify whether male vs female or vice versa
Caro, Salas, et al (1999)	Kaplan-Meier, log-rank test	Logistic for 12 mo persistence		OR Age >60 y 1.11, female 1.16, established HT 10.73, >3 other medicines 1.29, >5 GP visits 1.59, hospital admission 0.75		Log-rank test for new vs established HT significant p < 0.001
Caro, Speckman, et al (1999)	Kaplan-Meier, log-rank test for drug class	Logistic for 12 mo persistence	Age, sex, GP visits, other medicines, hospitalization	OR (95% CI) Diuretic 1.00, BB 1.25 (1.12, 1.39), CCB 1.51 (1.36, 1.69), ACE 1.92 (1.76, 2.09)		Log-rank test for drug class significant p < 0.001
Benson et al (2000)		ANCOVA for median duration between drugs		Men significantly longer therapy overall and for atenolol, quinapril, HCTZ + triamterene	Drug type	Duration difference men vs women may not be clinically significant
Dezii (2000)	% persistent plotted vs month			Test single tablet vs 2 separate drugs at 6 and 12 mo; test not stated but significant (p < 0.05)		
Bourgalt et al (2001)	Cox PH for time to first modification of initial therapy	Poisson regression for modification rates		Age inc, female inc, BB vs others dec, combination vs others inc		Hazard ratios not given in paper
Conlin et al (2001)	% persistent each 6 mo plotted vs time	OLS regression for difference in persistence rate over time (12–48 mo)		Predicted difference in persistence rates vs AT2s: Thiazide –68.8%, BB –34.5%, CCB –20.8%, ACE –10.1%; p < 0.001		Log transform persistence rate
Ren et al (2002)		OLS regression for compliance (over 2 y)		Predictors of compliance: age inc, nr of medications inc, input to treatment decisions inc, doctor age dec, speciality care resident vs primary care, other healthcare provider vs doctor	Race, education >13 y, doctor's sex, practice size	
Degli Esposti E et al (2002)	Cox PH for duration first–last prescription			Hazard ratios for discontinuation: age (1 y) 0.976 (0.974, 0.978), female 0.894 (0.832, 0.961), diuretic 2.624 (1.992, 3.457), BB 1.869 (1.414, 2.472), CCB 2.073 (1.574, 2.731), ACE 1.577 (1.198, 2.076), AT2 1.00, GP age 1.006 (1.002, 1.011), GP female 0.911 (0.836, 0.992)	Comorbidity, previous hospitalization, district, practice size	Patient age then drug class have most influence on persistence
Marentette et al (2002)	Persistence plotted vs time for drug classes	Repeated measures ANCOVA for relationship between drug class and persistence		Age, female, drug class – all pairwise comparisons significant except CCB and BB, female · drug class, age · drug class		Increasing age increases persistence, mainly because younger patients especially taking BB, CCB, diuretics

continued overleaf

Table 3 *continued*

Reference	Survival analysis	Other analyses	Control	Significant	Nonsignificant	Comments
Wang et al (2002)		Ordinal logistic regression for PDC tertiles	Age, sex, race, education, employment, treat site, thiazide use, comorbidities	OR (95% CI) Depression (1 point on 15-point scale) 0.93 (0.87, 0.99), external locus of control (6-point scale) 1.15 (0.99, 1.33)	Health beliefs, knowledge of HT, social support, satisfaction, alcohol use, smoking, socially desirable responding, depression diagnosis	
Hasford et al (2002)	Kaplan-Meier for differences in drug classes Cox PH for time on initial monotherapy			Hazard ratios not given Patients on irbesartan significantly more likely to persist with initial therapy than all others		
Degli Esposti L et al (2002)	Cox PH for time to discontinuing initial AHT (additions included) PH assumption tested	ANOVA to compare patient ages in continuers, switchers, discontinuers and in drug classes		Hazard ratios for discontinuation: age (+1 y) 0.982 (0.981, 0.983), AT2 1.00, diuretics 2.442 (2.044, 2.917), BB 1.525 (1.272, 1. 829), CCB 1.913 (1.602, 2.284), ACE 1.695 (1.419, 2.025), heart disease 1.531 (1.238, 1.894), diabetes 1.509 (1.242, 1.834), previous CVD hospitalization 1.524 (1.394, 1.667), ≥2 comorbidities 1.571 (1.334, 1.851)	Sex, asthma drugs	
Wogen et al (2003)	Cox PH for time to discontinuation of any AHT	OLS regression for compliance (PDC)		Hazard ratios for discontinuation: p < 0.0001 in all cases unless stated: age 0.933, male 0.954, valsartan 1.00, amlodipine 1.333, lisinopril 1.446, diuretics 1.103, diuretic combination 1.544, BB 1.131, nitrates 1.137, LLDs 0.743, chronic disease score 1.013, digitalis 1.049 (p = 0.0012), antiplatelets 1.032 (p = 0.018)		
Taylor and Shoheiber (2003)		No modeling; chi-square and t-tests	Stratified for age group; morbidity score (Charlson index)	Amlodipine/benazepril vs ACE + CCB		Sequential prescriptions of ACE, CCB considered for MPR
Degli Esposti et al (2004)	Cox PH for time to discontinuing initial AHT	OLS regression for costs		Hazard ratios for discontinuation: age (+1 y) 0.978, diuretic 1.853, CCB 1.663, ACE 1.386, AT2 1.00, heart disease 1.666, diabetes 1.394, previous CVD hospitalization 1.507, ≥2 comorbidities 1.630	Sex, asthma drugs	

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; BB, β-blocker; CCB, calcium channel blocker; AT2, angiotensin-II antagonist; AHT, antihypertensive; LLD, lipid-lowering drug; CVD, cardiovascular disease; HF/CHF, heart failure; CAD, coronary artery disease; HT, hypertension; COPD, chronic obstructive pulmonary disease; LVH, left ventricular hypertrophy; AMI, acute myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack; PDC, proportion of days covered; MPR, medication possession ratio; OLS, ordinary least squares; PH, proportional hazards; ANCOVA, analysis of covariance; ANOVA, analysis of variance; OR, odds ratio; CI, confidence interval; dec, decrease; inc, increase; mo, month; y, year.

antihypertensive therapy, and other variables (Monane et al 1997). Ordinary least squares regression was used to model compliance as a continuous variable, usually calculated as the medication possession ratio, in terms of covariates (Rizzo and Simons 1997; Conlin et al 2001; Ren et al 2002). Simple survival analysis methods, notably the construction of Kaplan-Meier curves showing the proportion of patients still taking their medications plotted against time, attempt to illustrate the time dependence of the outcome (Caro, Salas, et al 1999; Caro, Speckman, et al 1999; Dezii 2000; Conlin et al 2001; Hasford et al 2002). Survival analysis in this context is based on the probability that individuals still receive their prescriptions at various points in time. One of

the earliest studies to use Cox proportional hazards modeling (Hosmer and Lemeshow 1999), a regression method for modeling survival data, to assess duration of therapy in terms of covariates was based on Canadian data (Bourgalt et al 2001), and several subsequent studies used the same type of analysis (Degli Esposti E et al 2002; Degli Esposti L et al 2002; Gregoire et al 2002; Hasford et al 2002; Wogen et al 2003). These did not all make full use of the capability of this type of modeling to deal with censored observations (observations that do not have complete follow-up data). In this context, there are two problems with Cox models that were not adequately addressed. One is that it is assumed there are no time-dependent covariates. Another is that where

the data are available on a monthly basis, as is often the case with prescription claims, the model must be adapted to deal with the fact that durations of prescription availability are discrete rather than continuous.

Adherence rates

Tables 2 and 3 summarize the findings from individual studies. The 1-year adherence rates are shown (where available) for selected studies in Table 2. These adherence rates are based on the outcome measures as defined in individual studies. From one database, they range from 33.8% of patients having made no modification of treatment at 1 year (Bourgalt et al 2001) to 78% of new users of antihypertensives persisting with treatment at 1 year (Caro, Salas, et al 1999). Interestingly, these results were based on patient populations drawn from the same database, Saskatchewan Health, which emphasizes the importance of patient selection and outcome definitions. Bourgalt and colleagues included all patients who were new to antihypertensive therapy and observed for at least 1 month after the initial prescription (so that patients who left the scheme were treated as censored and included in the analysis) and the outcome was any modification in treatment, which included treatment gaps, discontinuations, and addition or substitution of drugs. Caro, Salas, and colleagues included patients who were new users of antihypertensives and were observed for at least 1 year from the inception date (ie, censored patients were excluded). These patients were considered persistent if their final prescription, which could be for any antihypertensive drug, covered the period until the end of the observation year. There are several reasons for the discrepancies in reported results. One is the selection bias resulting from the exclusion of patients who left the scheme during the observation year. Another is the definition of the adherence outcome to include prescription of any antihypertensive drug at the end of the year (ie, switches included; Caro, Salas, et al 1999) as opposed to the initial monotherapy (ie, any type of modification classified as nonadherence with the initial therapy; Bourgalt et al 2001).

Demographic factors

Table 3 shows significant and nonsignificant factors associated with adherence outcome measures. There are some inconsistencies in the results, especially with regard to the association of demographic factors such as age and sex with outcomes. Some studies find women more

persistent (Caro, Speckman, et al 1999; Conlin et al 2001), two find men more persistent (Benson et al 2000; Wogen et al 2003), and some find no difference in outcome rates between men and women (Rizzo and Simons 1997; Degli Esposti L et al 2002). Some find no relationship with age, while others find older patients more likely to adhere with their antihypertensive therapies (Rizzo and Simons 1997; Bloom 1998; Caro, Speckman, et al 1999; Conlin et al 2001; Degli Esposti L et al 2002; Ren et al 2002; Wogen et al 2003). Age is often dichotomized, a typical cut-off point being 65 years, though in some studies it is included as a linear variable (Degli Esposti L et al 2002; Wogen et al 2003). However, the nature of the association is not further explored. In any case, the relationships with these factors are relatively weak and should be interpreted with caution.

Other patient factors

Two of the studies used patient interviews as well as prescription data. One study found an association between increasing depression symptom severity and compliance with antihypertensive therapy; however, it failed to find any association between health beliefs, knowledge of hypertension, social support, or satisfaction with care and compliance (Wang et al 2002). The other found that patients who were involved in treatment decisions were more likely to be compliant ($r = 0.64$) (Ren et al 2002).

Healthcare system factors

Several studies investigated aspects of the relationship between patients and the healthcare system. The number of visits to the doctor was found to have a positive association with the adherence measure (Jones et al 1995; Monane et al 1997; Caro, Salas, et al 1999). Two studies found that younger doctors tended to have more adherent patients (Degli Esposti E et al 2002; Ren et al 2002). One study found that patients treated by nurses or physicians' assistants were more likely to be compliant than patients treated by physicians (Ren et al 2002). Patients who had previously been hospitalized were found more likely to be persistent with antihypertensives in large Canadian and Italian studies (hazard ratio = 1.52; p < 0.05) (Caro, Salas, et al 1999; Degli Esposti L et al 2002), but an investigation using a smaller sample from the same Italian population found previous hospitalization to have no association with persistence (Degli Esposti E et al 2002). One study found that patients who did not collect all their antihypertensive prescriptions from the same pharmacy were less likely to be compliant (odds

ratio [OR] = 0.4; p < 0.05, for visiting > 1 vs single pharmacy) (Monane et al 1997).

Therapeutic regimen factors

Complexity of the therapeutic regimen is known to have a negative effect on adherence. Two studies found that patients taking a medication as a combination tablet were more persistent with that treatment than patients who took two separate tablets (Dezii 2000; Taylor and Shoheiber 2003), while another found that taking more than one dose per day had a negative effect on persistence (OR = 1.40; p < 0.05) (Bloom 1998).

Some authors used information on other prescriptions for therapies other than the antihypertensives of interest either to select patients or to include as covariates in models for adherence. There was conflicting evidence on the influence of co-prescriptions on adherence. Prescription of a large number of other medications was found to have a negative (large defined as more than eight medications) and also a positive (large defined as three medications) effect on adherence outcome rates (Monane et al 1997; Caro, Salas, et al 1999; Ren et al 2002). Similarly, a high chronic disease score (Wogen et al 2003) or evidence of two or more comorbidities (Degli Esposti L et al 2002) reduced the risk of discontinuation. Specifically, patients with evidence of heart disease and diabetes were found to be more persistent (Degli Esposti L et al 2002), as were patients with heart failure (Rizzo and Simons 1997).

Several studies set out to examine whether there were differences in adherence rates between drug classes. Although one study found no difference (Benson et al 2000), most concluded that patients were least likely to adhere with diuretic therapy, followed in various order by β-blockers, calcium channel blockers, ACE inhibitors, and angiotensin-II antagonists (Rizzo and Simons 1997; Bloom 1998; Caro, Speckman, et al 1999; Conlin et al 2001; Degli Esposti E et al 2002; Degli Esposti L et al 2002; Hasford et al 2002; Wogen et al 2003). However, this may be due to patient selection rather than an effect of the particular therapies.

Discussion

This review has shown that there is a wide variability in the rates of nonadherence with antihypertensive therapies, but most of this variability is due to differences in methods and definitions used in the various studies. Owing to lack of comparability, no meta-analysis, combining results from the various studies, was attempted.

Prescription databases give no information on the pattern of drug ingestion on a daily basis. They provide information on drug supply; patients are unlikely to continue collecting prescriptions if they have stopped taking their medicines. In some cases, for instance in health insurance schemes, patients may collect their prescriptions and hoard their medicines, but we have no evidence to suggest this. Prescription databases provide information on what prescriptions were collected but not what was actually prescribed by the doctor or consumed by the patient, so that for the assessment of adherence the assumption is made that the medicine type and quantity received is exactly what was prescribed. In particular, it may not be valid to assume the daily dose prescribed. When attempting to quantify adherence, the most appropriate use of these data is to ascertain discontinuations and changes of therapy. To do this, it is necessary that all prescriptions collected by the patient during the time of observation are included in the database. Analysis methods that allow for censored observations can be used to include information on patients who leave the scheme before the end of the observation period. There is less justification for using prescription refill data to estimate percentage levels of patient adherence. As it is typically estimated over a year, a percentage estimate of adherence takes no account of the longitudinal structure of the data. Thus an estimate of the adherence of a patient who fails to collect a prescription in the third, fifth, and ninth months will be the same as for one who collects prescriptions continuously for 9 months and then stops.

Previous reviews of the assessment of adherence using prescription databases have made some important observations on the scope and limitations of this approach, which have often not been adequately addressed in subsequent studies (Steiner and Prochazka 1997; Payne and Esmonde-White 2000). Since these reviews were published there have been advances in the application of modeling techniques, notably the use of more sophisticated survival techniques such as Cox proportional hazards modeling.

Methods of analysis that choose a single point in time for the outcome and require that all patients must be observed until this point may introduce selection bias and do not allow for any modeling of patterns of prescriptions received over time. Survival analysis methods, such as the Cox proportional hazards model, allow the inclusion of patients who are not observed over the entire time period and can be used to analyze continuous prescription refills over time. But as noted above, the Cox model assumes proportionality of baseline hazards (ie, the baseline risk is proportional to

time) and is perhaps not the best way of dealing with time-dependent covariates. It also assumes continuous time, so that where prescriptions are dispensed monthly (ie, on a discrete-time basis), there may be problems with multiple ties in the survival times. A model allowing for discrete survival times may be more appropriate.

Many of the studies on this topic seem to rework the same ground without providing new insight and perhaps perpetuate the same flaws in design, analysis, and interpretation. The contribution they make is to reinforce the point that nonadherence rates are very high. Rather than additional large cohort studies, attention should focus on the appropriate design and methodologies of these studies. The analyses used in previous studies are mostly rudimentary, and conclusions drawn may be unjustified. One particular problem is that the studies are observational in nature and there are inherent biases associated with this; for example, individual characteristics that may affect drug adherence may also have an association with the type of drug prescribed.

This is not considered in most studies. For instance, the better compliance rates for angiotensin-II antagonists are attributed solely to characteristics of the drug (particularly the placebo-like adverse effect profile). But the relationship between adverse effects and discontinuation is not fully understood and appears to depend upon context. According to a meta-analysis of clinical trials, approximately 3.1% of patients treated with angiotensin-II antagonists or diuretics will discontinue therapy because of adverse effects (Ross et al 2001); however, in the observational studies examined here, 33%–67% of patients starting an angiotensin-II antagonist and 62%–79% of patients starting a diuretic had discontinued their initial treatment by the end of the first year. A Canadian study that followed 682 patients who were newly prescribed antihypertensives found that 62% reported adverse effects and 50% of these discontinued their initial therapy, in comparison with a 31% discontinuation rate among patients who did not report adverse effects (Gregoire et al 2002). A Japanese questionnaire-based study found 49% of patients with well controlled blood pressure reporting adverse effects with their antihypertensive medicines and a statistically significant relationship between the number of reported adverse effects and nonadherence (Toyoshima et al 1997). However, it has been observed elsewhere that patients who discontinue are less likely to respond to questionnaires (Suarez et al 2000), so that the results of this study should be interpreted with caution. Certainly it is known that polypharmacy increases the risk

of adverse effects due to drug interactions. It has been observed that patients who are more ill, and therefore are prescribed more drugs, are also more likely to adhere with their treatment. There are many complex interacting factors that affect patient adherence; quantification of these remains a problem.

The results reported in the observational studies tabulated here should be interpreted carefully in terms of context, patient and regimen selection, and definitions of adherence. There is a need for more sophisticated statistical modeling appropriate to the discrete-time longitudinal structure of the data. Given that prescription refills are effectively repeated measures on individual patients, random effects models, incorporating patient-specific variability, may give further insights into the patterns of antihypertensive use at the individual level (Goldstein 2003).

Acknowledgments

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