Compliance of Hypertensive Patients with Pharmacological Treatment

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SUMMARY Failure of compliance with drug treatment is a major problem in all diseases requiring long-term therapy. The incidence of noncompliance is variously reported as between 5% and 60% in well-conducted investigations in hypertensive patients. Direct (objective) methods give a higher incidence of noncompliance than indirect (subjective) methods. Among factors associated with noncompliance, the complexity of the treatment regimen and the nature of the doctor-patient relationship are important; few demographic characters among the patient population can be identified. Improvement of noncompliance depends on understanding these facets of the problem.


KEY WORDS • patient compliance • blood pressure control • compliance measurement

COMPLIANCE can be defined as the extent to which a patient's behavior coincides with medical advice. This advice can be related to medication, diet, smoking, or any lifestyle change. The present review is limited to compliance with drug treatment.

Poor compliance is one of the largest problems in therapeutics. A contrary view was put forward in a recent editorial that somewhat surprisingly expressed the sentiment that, since doctors can be wrong in their diagnoses, their instructions are sometimes best ignored. This article equated the consequences of poor compliance with drug treatment in patients on long- and short-term therapy, and this is a prevalent error. In reality, failure of the hypertensive to take medication has profound short-term as well as long-term consequences (i.e., failure to take two or three doses of a drug such as clonidine may result in a medical crisis). On the other hand, 3 days of antibiotic therapy in a patient with acute urinary infection, instead of the prescribed 10, may be quite sufficient to cure the condition and may, in fact, be more beneficial than the longer duration of treatment.

Compliance is especially difficult to achieve in hypertensive patients who are asymptomatic prior to the start of treatment. Continuing compliance will depend on the patients' perceptions of the benefit that treatment will confer. If there had been symptoms such as severe headaches that were abolished by drug therapy, it is reasonable to assume that the patients would be likely to continue the drugs, especially if their symptoms returned on withdrawal of drug treatment. Previously well patients, however, may only feel the adverse effects of the administered drugs and not realize their long-term benefits depending on their level of information. Asymptomatic hypertensive patients are in a more difficult position than many other groups of patients who may require long-term therapy in another respect. The epileptic, diabetic, or asthmatic will soon know about the dangers of poor drug compliance, whereas the mild hypertensive may only realize its consequences after months or years.

Resistant hypertension may be the result of poor compliance. It can be defined as raised blood pressure that does not respond to therapy with standard drug treatment. Since this definition presupposes compliance, however, compliance should first be ascertained before unnecessary investigations of other underlying causes. The recently published 5-year findings of the Hypertension Detection and Follow-up Program demonstrated that an aggressive organized program of hypertensive care can control blood pressure in two-thirds of hypertensives; little is known of the factors causing poor control in the remainder, but failure of compliance is probably one of the more important.

A model that can help clarify the role of compliance and other factors in the control of elevated blood pressure has been proposed. Cross-classification of treated patients by compliance and blood pressure control results in four groups that highlight potential problems in hypertension treatment: 1) the compliant, controlled group, which presumably represents the ideal treatment state; 2) the compliant, uncontrolled group, which includes persons inadequately treated with inap-
propriate drugs, or with appropriate drugs given in the wrong dosage, or whose blood pressures are less amenable to drug treatment because of factors such as secondary hypertension and drug interactions; 3) the noncompliant, controlled group, which includes hypertensives whose blood pressures are controlled despite noncompliance or those subjected to overtreatment or unnecessary treatment due to misdiagnosis; and 4) the noncompliant, uncontrolled group, whose blood pressure is uncontrolled due to failure to take medication.

**Extent of Noncompliance**

It is difficult to assess the size of the problem of noncompliance. Many studies assessing its incidence are themselves frequently flawed by poor design. Various authors (for review, see Evans and Spelman4) have estimated the incidence of noncompliance in different diseases requiring long-term drug treatment as 5% to 80%. These differences depend among other things on the definition of noncompliance, the nature of the illnesses studied, and the arbitrary duration of long-term treatment. Most studies have addressed themselves to the study of compliance to psychiatric drug treatment and fewer to problems of compliance in hypertension.

In a study of 185 patients admitted for surgery, 51 were either hypertensive or had a history of hypertension.3 Of 26 currently hypertensive patients in this series, eight had discontinued medication, giving an incidence of noncompliance of 31%. This study illustrates another aspect of poor compliance. Patients may stop drug treatment on their own initiative because of a lack of understanding of the nature of disease and its treatment, because of the inefficiency of the medical service in recalling patients for follow-up, or because the medical practitioner is not aware of the need for long-term treatment. In another study aiming at a definition of the role of the clinical pharmacist in improving drug compliance in hypertension, two groups of patients were studied, only one of which was given the benefit of clinical pharmacy advice.6 Noncompliance with drug treatment was found in some 84% of the control subjects. Compliance was rigorously defined in this study as the ratio of the number of doses administered to the number of doses prescribed. This study again highlighted the prevalence of poor education and poor understanding of hypertension and the importance of therapy. Caldwell and colleagues,7 in a follow-up of 76 hypertensive patients, found that by 11 months half had dropped out of the treatment program and only 17% were still on therapy 5 years later. Finnerty et al.8 found in a Washington D.C. population survey that only 50% of the hypertensive patients kept one follow-up clinic appointment. Wagner and colleagues found that 74% of 385 treated hypertensive patients complied with therapy, compliance being assessed by questioning the patients. The main factor determining compliance in this series was the complexity of the medication regime; no patient demographic characteristics indicated the compliers. Further, diastolic blood pressure control was significantly better in compliers than noncompliers, but even in admitted noncompliers, good blood pressure control was frequently found, raising the possibility of overtreatment or unnecessary treatment.

Data for compliance obtained from specialized hypertension clinics are more optimistic; dropout rates of between 3% and 20% are recorded in various series (reviewed by Sackett and Haynes3).

In comparison with other cardiovascular disorders, it has been estimated that noncompliance with anticoagulant therapy occurs relatively infrequently. Van Gastel and colleagues10 used serum drug monitoring as the method of assessing compliance and found acceptably low serum phenprocoumon levels relative to administered dose in only 11 of 225 patients (4.9%). In digitalis therapy, however, we described 198 of 403 (49.1%) patients whose serum digoxin levels on two separate occasions were unacceptably low despite alleged long-term digoxin consumption.11 When digoxin was stopped in 94 of these patients, not one patient apparently suffered any adverse consequence of stopping medication, leading to the conclusions that not only was noncompliance common (because of the low serum digoxin levels) but digoxin therapy itself was probably unnecessary.

**Methods of Assessing Compliance**

There are two broad methods of assessing compliance with drug therapy. Direct or objective methods are those in which the drug can be identified in the patient; indirect or subjective methods include those where there is an assessment either by the patient or some other individual as to whether the medication has been taken. Direct methods generally give higher figures for noncompliance than indirect methods.4

**Direct Methods**

**Blood Level Monitoring**

The substance monitored may either be the drug itself, a drug metabolite, or a marker introduced into the tablet but with no therapeutic properties. If there is a clear relationship between drug dose and steady-state plasma drug levels, a good indication of the degree of compliance can be gauged. Where interindividual differences in drug handling occur, a quantitative assessment of compliance is more difficult. Thus, the results with respect to phenprocoumon compliance discussed above10 must be interpreted with caution. In hypertension, few clinicians measure blood levels of antihypertensive drugs on a routine or even semiroutine basis since the pharmacodynamic endpoint (e.g., blood pressure) can be monitored so easily, and little if any data exist on assessment of compliance in hypertension using this method.

**Measurement of Urine Drug Excretion**

This has been used extensively as a method of assessing compliance with antipsychotic drugs.4 Lowenthal and associates12 tested the urine from hy-
pertensive subjects to monitor their adherence of a regime containing thiazide diuretics. They found that two-thirds of the patients had measurable drug concentrations in their urine and they were three times more likely to have "goal" blood pressure levels than the one-third of patients with negative results. This method obviously gives a semiquantitative measurement of compliance.

Indirect Methods

Pill Counts

This employs the stratagem of asking the patient to return a medication container at regular intervals and the number of tablets not used forms the basis for an assessment of compliance. Inherent in this method is the practice of giving patients a variable number of tablets more than they require. This method is widely used in hypertension studies, but suffers from the drawback that the determined noncomplier may willfully dispose of tablets by methods other than consuming them.

Questionnaires of Patients or Associates

Bulpitt and his colleagues\textsuperscript{13} used a questionnaire to assess the incidence of over- and underconsumption of antihypertensive drugs. Of 817 patients questioned, 10\% reported they were taking fewer tablets than they should, and 7\% were actually taking more. This incidence of noncompliance was surprisingly low and was varied with different forms of medication (see below). Asking patients, their relatives, or medical attendants about noncompliance is fraught with difficulties. It has been stated that the more senior the physician, the more likely is he or she to over-estimate compliance in patients, i.e., the more likely are patients to try to please physicians by giving appropriate responses.\textsuperscript{14}

Outcome of Therapy and Presence of Side Effects

In broad terms, the outcome of therapy can be used to assess whether the hypertensive patient has complied with therapy, but this is a crude measurement at best. The presence of side effects, or pharmacological effects of administered drugs is somewhat better. For example, in a patient prescribed a beta-adrenoceptor-blocking drug, an exercise heart rate of over 100 signifies inadequate beta-blockade, one important cause of which is non-compliance. The failure to find a dry mouth in a patient taking clonidine is also suggestive of poor compliance, especially if the blood pressure is inadequately controlled. In both examples cited, beta-blocker and clonidine, the pharmacodynamics of interindividual drug response may be confused with noncompliance.

Factors Associated with Noncompliance

Patient Characteristics

It is not easy to show any strong association between patient characteristics and compliance. An early review suggested that the noncompliant patient was more likely to be older, female, of lower economic status and educational attainment than the compliant patient; considerable doubt has now been cast on this.\textsuperscript{4} Bulpitt et al.\textsuperscript{13} found that the "obsession score" (measured by questionnaire) was lowest in noncompliant hypertensives but, interestingly, found that overconsumption of tablets was nearly as big a problem as underconsumption in obsessives. Studies of psychiatric patients\textsuperscript{4} have suggested that patient's attitudes toward authority are important. Errors and noncompliance probably do occur more frequently at the extremes of age; in the young, the mother's view of the severity of the illness is an important factor in determining compliance.\textsuperscript{15} At the other age extreme, geriatric patients pose problems because of lapses in memory and self neglect.

The current disaffection with allopathic medicine and the increase in popularity of alternative forms of therapy encourages noncompliance. The patient who prefers to "do it alone" and not to rely on drug treatment is always a potential noncomplier. In hypertension, until nondrug methods of controlling blood pressure have greater credence and applicability than today, alternative approaches to treatment should be treated with great caution.

Two statements sum up the situation. Blackwell\textsuperscript{15} says that every patient is a potential defaulter and compliance can never be assumed, while Sackett\textsuperscript{16} expressed the view that clinicians cannot outperform the toss of a coin in predicting which patients will comply with therapy.

Disease Characteristics

Noncompliance with drug treatment has been shown to be a problem in all diseases, irrespective of its severity or duration. Certain diseases influence the patient's awareness of the need to comply, such as the hypomanic patient who no longer entertains the idea that treatment for his condition is necessary. However, even in diseases such as tuberculosis, a range of noncompliance from 30\% to 72\% of the patients has been documented.\textsuperscript{4} If failure of compliance to long-term treatment is likely to lead to short-term problems (e.g., asthma, diabetes, epilepsy), it might be thought that compliance is likely to be better than where the opposite situation pertains. The patient's perception of the severity of the illness is important, and this probably depends on doctor-patient relationships more than any other single factor. How hypertension is viewed clearly depends on this aspect, as well as the patient's symptoms.

Treatment Characteristics

The longer a patient has already been on treatment the more likely is he to comply with therapy.\textsuperscript{3} Thus, the incidence of noncompliance is likely to be higher if studied earlier rather than later in the course of therapy. The majority of treatment failures from noncompliance occur within the first few months.

It has been shown over many years by many investigators that the simpler the drug regime the more likely the patient is to comply.\textsuperscript{3,4} This is of special relevance with respect to hypertension and the recent introduc-
tion of once-daily medication regimens such as slow release formulations of β-adrenoceptor-blocking agents and combination therapy. It is difficult to find good evidence that compliance is better with a once then twice-daily regime, but when a drug needs to be administered three or more times daily, the incidence of noncompliance usually rises steeply.\textsuperscript{16} Gatley showed that the number of defaulters doubled when the number of tablets was increased from one to four.\textsuperscript{17}

The nature of the medication given for hypertension as a factor in compliance has also been investigated.\textsuperscript{13} There appeared to be little difference in noncompliance between methyldopa, bethanidine, guanethidine, or propranolol, all of which produced a considerable number of adverse effects albeit of a quite different nature. Compliance was much better with diuretics (1%-5% noncompliant), and this was associated with fewer side effects. Broadly, similar conclusions were reached by Nies\textsuperscript{8} in another study of hypertensive patients.

The cost of medication is important in compliance. High cost may prevent the patient purchasing the medication, but whether having bought them it encourages him to take the drugs is not certain.

Doctor-Patient Relationship Characteristics

Noncompliance is most commonly due to failure of the patient to comprehend the need for drug treatment frequently because he feels well without the drug, to willful noncompliance, or to forgetfulness. Good doctor-patient relationships have an important role in improving each of these. If communication between doctor and patient is effective, the incidence of noncompliance is likely to be small. Rosenberg\textsuperscript{19} suggested that it is not the relationship which is created at the first visit to the doctor which determines good compliance, but a regular, effective contact. Ley\textsuperscript{20} showed that patients quickly forget advice given by doctors, and that regular reinforcement of instructions, carried out in a pleasant manner, preferably using written instructions, is likely to be reciprocated with good compliance. Enthusiasm on the part of the doctor is important; a passive doctor who accepts authoritative behavior is likely to promote noncompliance. In a contradictory study, Sackett, Haynes and colleagues\textsuperscript{21} investigated the importance of an educational program in improving compliance in 230 Canadian steelworkers. They found, somewhat surprisingly, that although the patients learned a lot about hypertension, they were not more likely to take their medicine than a control group not exposed to this information. In a second phase of the same study, however, when home blood pressure monitoring was instituted in the noncompliant, compliance increased by some 20%.\textsuperscript{16}

Improvement of Compliance

It is better to avoid the problems of noncompliance than to face its consequences. This involves three stratagems: 1) recognition of the “at-risk” patient; 2) thoughtful treatment planning; and 3) proper explanation to the patient.

Recognition of the “At-Risk” Patient

Patients at risk include those all with chronic illness requiring long-term therapy, and the ill effects of stopping which may be remote rather than dramatic and rapid. Hypertension clearly falls into this category. Children and the elderly can cooperate less well. Patients who are not well disposed toward their medical attendants are likely to be noncompliers. A familiar, well-liked physician, who himself believes in the appropriateness of the prescribed drug treatment appears to be a good guarantor of compliance.

Treatment Planning

A minimum number of drugs should be prescribed. Drug combinations (e.g., beta-blockers with diuretics) can be used with advantage to improve compliance in the patient at risk, and these can be recommended if the ingredients are therapeutically appropriate. Calendar packs, dose dispensers, and improved labelling have their place in encouraging compliance. Sustained release formulations by permitting less frequent dosing are also to be recommended.

Explaining Treatment

The work of Sackett and his colleagues\textsuperscript{21} on the failure to improve compliance in Canadian hypertensive steel workers by means of an educational program questions the basis of giving the patient adequate information about his disease and his drug treatment. It would appear to be important to confirm or refuse these findings in a different setting. It is also important, in our view, to discuss with the patient, the question of the duration of treatment. It is my practice to tell the patient that treatment may continue for several years, but that this will be reviewed at regular intervals. To state that treatment will be “life long” is both potentially discouraging to many patients and inaccurate since much work is currently being carried out on the possibility of stopping drug therapy in selected patients. Other members of the health care team — especially nurses and pharmacists — have an important role in promoting compliance.\textsuperscript{6} When the hypertensive patient returns for a repeat prescription, his blood pressure should be checked and the message of compliance reinforced.

Conclusions

Doctors should be aware of the problem of noncompliance and its consequences in their hypertensive patients. Drug regimens should be kept as simple as possible and directions as clear as we can make them. The fewer the medications, and the less often they need to be taken, are important considerations. Human frailty being what it is, people will make errors anyway. Patients, doctors and nurses are all prone to error in drug administration and, if a patient is not responding to treatment, investigation of the possibility of noncompliance is mandatory, and possible reasons for this unearthed. It seems reasonable that doctors and other health care staff should talk to patients about drug treatment. It may be that, in some patients, long-term
antihypertensive therapy is unnecessary and this aspect merits serious investigation. It may emerge that the only way of ensuring compliance is to make the medication addictive and this brings its own complications and problems.

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Discussion

DISCUSSANTS: F. GROSS
A. BRECKENRIDGE
W. VETTER
J. MENARD
F. DIENSTL

GROSS: The number of tablets or applications taken over the day has been thought to be of major importance in compliance, and you mentioned the sustained-release, once-daily formulations. But are you convinced that reducing the number of daily doses is of major significance for improving compliance?

BRECKENRIDGE: This is a very soft subject . . .

GROSS: because there are very few data . . .

BRECKENRIDGE: and very bad data at that. But the results, largely from psychiatric therapy rather than antihypertensive therapy, indicate that if medication can be reduced to twice a day then compliance may be improved — and if this entails making a sustained-release preparation, that is a reasonable strategy.

MENARD: You mentioned that education or income has no effect on compliance, but some studies have shown a link between low educational standards and low attendance at a clinic — and we found a similar relationship with low income. Similarly, other factors include obesity and smoking, which are also linked with a lower attendance at a hypertensive clinic.

BRECKENRIDGE: For education, I could quote six or seven studies agreeing with what you said, and another seven or eight that entirely disagree. I

suspect that there must be regional or other differences.

DIENSTL: Another factor that should be added to your nice table of the low compliant who achieves the therapeutic aim is the placebo effect.

BRECKENRIDGE: Yes, I agree.

DIENSTL: How highly does self-measurement of blood pressure influence compliance in antihypertensive treatment?

BRECKENRIDGE: Sackett has claimed an increase of 50%, but I think one has to be very careful about whom one prescribes such a machine for; it may come to dominate a patient’s life. Patients may measure their own blood pressure 15 times a day unless instructed otherwise.

GROSS: It’s a small percentage of patients who become neurotic, however.

BRECKENRIDGE: I’ve seen quite a number myself.

VETTER: Is it a good policy to try to identify potential poor compliers?

BRECKENRIDGE: There are important guidelines. For example, in childhood the most important factor is the mother’s attitude toward medication, as shown in studies on compliance with antibiotics. For specific groups, such identification might be important.
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