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Patient compliance with drug treatment – new perspectives on an old problem

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Summary. Compared to other variables being considered in therapeutics, patient compliance has long been given minor attention although it affects every aspect of medical care. Limited methodology of compliance measurement, in particular, has hampered major progress in research, and pre-conceptions have been reiterated. However, there is a recent surge in interest derived from new data revealed by reliable methods, i.e. continuous medication (compliance) monitoring. The visualization of dynamics in drug regimen compliance over time offers unique opportunities, both to scientific drug evaluation and therapeutics in medical practice. New perspectives related to the descriptive and explanatory side of the problem are outlined by giving examples from various therapeutic fields.

Key words: Patient compliance – Compliance monitoring – Drug evaluation

Although patient compliance is hardly a new problem, there has been a surge of interest in this field in the past few years, reflected by scientific meetings, new books, editorial comment, and many papers in peer-reviewed journals [1, 2, 6, 10, 12, 14, 17–19, 31, 34, 37, 39, 42, 48, 50–53, 57]. Patient failure to comply with prescribed regimens affects every aspect of medical care. Noncompliance is not restricted to ambulatory care settings, but also occurs among inpatients, as reported from studies which included more than 1200 hospitalized patients [20, 23]. Furthermore, compliance problems cut across all ages, from pediatrics through midlife to old age. However, compared to other variables being considered in therapeutics, compliance has often been given less attention or has even been neglected, both in medical practice and in controlled clinical trials.

Dedicated to Prof. Dr. Dr. h.c. mult. Gotthard Schettler on the occasion of his 75th birthday

Why the recent surge in interest? The reason is that reliable methods have finally come to this age-old problem, bringing new data, and new perspectives in light of the data, instead of repetition of preconceptions. The lack of adequate measurement methods, in particular, has hampered major progress in compliance research, with regard to both descriptive and explanatory sides of the problem. Conventional methods do not provide information on the distribution of doses taken or omitted by patients. They cannot 'visualize' patients' drug use behavior over time; this would be possible only by continuous measurement.

First attempts, in the early sixties, to use automated devices for recording patients' dosing habits were not practicable because appropriate technology was not available, although first experience was promising. Nevertheless, the idea of continuous measurement has to be regarded as a breakthrough in compliance research [43]. Progress in microelectronic technology has facilitated the design of convenient and unobstructive systems by which continuous medication (compliance) monitoring over periods for up to several months is now realized [12, 34].

Medication monitoring of various types of medication in both long- and short-term treatment courses showed striking similarities in compliance distribution [12, 31, 37, 47, 50]. Partial compliance is the most frequently observed type of deviation from prescribed regimens.

There are certain patterns of drug use behavior, such as patient-initiated drug holidays and the 'toothbrush' or 'white-coat' effect which might have been suspected, but have never been revealed before by conventional methods [13, 31, 34, 47, 51]. For example, compliance increased significantly before clinical visits in patients treated with pilocarpine eye-drop medication, in patients treated for epilepsy, and in hypertensive subjects. During intervals, between visits to the doctor, or after discharge from the hospital, compliance – percentage of prescribed doses taken – declines, as has been

revealed, for example, with antiepileptic treatment, diuretics, cardiac glycosides, and lipid-lowering drugs.

Patient-initiated drug holidays, or days without drug use, appear to be a frequent phenomenon, often associated with such interruptions of daily habits, as holidays and weekends. Drug holidays may contribute substantially to compliance-related (re-)admissions to the hospital [56]. Consecutive drug holidays with diuretic therapy were followed by deterioration of congestive heart failure due to severe pulmonary congestion [34]. The majority of breakthrough seizures were closely associated with omissions of antiepileptic drugs [12]. Less spectacular, though of clinical relevance, is noncompliance with lipid-lowering drug therapy in patients with familial hypercholesterolemia [32]. Even with a once-daily regimen, high compliance cannot be guaranteed. The therapeutic effect of simvastatin, as measured by the decrease in LDL cholesterol, was subverted by partial compliance in one third of patients [35].

On the other hand, deviations from prescribed drug regimens may, in fact, protect patients from inadequate prescribing [58].

It is clear that compliance cannot be predicted exactly from knowledge of patient variables such as age, education, or socioeconomic levels, although many research efforts have focused on identifying the characteristics of those who comply and those who do not. Nevertheless, categorization of patient background problems, in a wider perspective, still appears to be attractive, particularly with regard to clinical trials. It is proposed by some experts as an important issue for future research [9, 11]. It is also clear that subjective estimates on compliance by physicians or other medical personnel are inadequate to offer a basis for compliance assessment [44, 45].

An adequate and reliable measurement technique is the prerequisite for both an assessment of the magnitude of the problem and an evaluation of interventional measures directed toward compliance improvement. In consequence, this holds true for investigations designed to study possible consequences of non-compliance [33].

There is, however, no perfect, 'gold-standard' method for compliance measurement [49]. Several limitations of conventional methods commonly applied have long been recognized and emphasized [22]. Those concerns have been clearly confirmed by the results of recent studies [48, 50]. Even so-called direct methods usually regarded as providing scientifically valid compliance information have their disadvantages and limitations [13, 41].

Whatever the definition of compliance, it will be closely related to the measurement method used [41]. In most studies, a simplistic approach has been applied, as by dividing patients into groups of compliant or noncompliant persons according to arbitrarily fixed cutoff points. Therefore, it is not surprising that compliance data relatively seldom corresponded to clinical measures such as blood-pressure reduction [5]. This may indicate the meaninglessness of the compliance definition used, which is partly due to inadequacies of the measurements that have been available. Furthermore, the dichotomous distinction between compliant and noncompliant patients simply does not take into account the variability of patients' drug use behavior. Compliance distributions have rarely been reported [21, 55]. Consequently, evaluation of the relationship between compliance and dose response is impossible.

This fact is relevant to the conventional interpretation of drug trial results, which merely focus on average effects. There is increasing concern and doubt about the value of the conclusions drawn from trial results with regard to true rates of efficacy and toxicity, and consequently to dosage recommendations delineated [4, 54].

In fact, inclusion of objective compliance data may contribute substantially to the interpretation of trial results [8, 30, 35, 40]. Provided these data are assessed by sensitive and specific methods, they may be employed as an explanatory supplement to the primary analysis [15, 25]. Correlation of compliance data with clinical effects, i.e., pharmacodynamics, may lead to a challenge of the appropriateness of therapeutic strategies such as dosage recommendations or the length of treatment courses [7].

There is increasing awareness of the need to adjust or tailor treatment according to disease patterns, a concept well known from chronopharmacology. For example, new insights into features of coronary artery disease and hypertension have led to a reevaluation of therapeutics with regard to the choice of drugs and optimal timing of dosage [24]. It appears likely that continuous compliance measurements, together with appropriate clinical assessment, will favorably contribute to drug evaluation. Furthermore, it appears reasonable to focus on various drugs which, by their duration of action, may be more or less sensitive to, or likely to compensate for, partial compliance [29].

Compliance monitoring, in its early stages, has been regarded as applicable and useful only in a strict research context [46]. However, its use need not necessarily be restricted to controlled trials.

In daily life, many patients execute 'noncontrolled' experiments by changing prescribed regimens, willingly or not [3, 34]. An example of a preconception is the view that patients will not accept compliance monitoring. However, previous studies and current work (unpublished data) revealed that a surprising number of patients not only accept, but welcome the process [3].

There is much to be learned from insights into patient behavior. In particular, there is a need for more knowledge about patients' reasons for deviation from prescribed drug treatment [36]. For example, patients may act or react 'intelligently' by reducing diuretic treatment from a prescribed once-daily to a once every-second-day regimen, or by temporarily increasing the dose of antiasthmatic treatment when breathing difficulties are exacerbated [34, 38]. Readily accessible compliance data might be a basis for discussion with patients – the first step for revealing and eliminating misconceptions, and consequently, for improving both the physician's treatment strategy and the patient's compliance behavior [9, 16, 27, 28, 42]. In 1979, Haynes stated that "compliance is one of the most guessed-about topics in health care" [26]. There is good reason to assume that this view will change remarkable. Nevertheless, there are many compliance issues still open to discussion and further study.

1. Compliance is variable, not dichotomous; arbitrary boundaries between good and not-good are meaningless and, in any case, drug-dependent.

2. Once-daily regimen is not necessarily the best.

3. Clinical judgment can probably detect the extremes of the very punctual and the terribly bad compliers, but cannot sort out good-enough from not-good-enough in the vast majority of patients.

4. With long-term treatment for asymptomatic conditions, the physician must distinguish between compliance problems and pharmacologic nonresponse.

5. No-dose days (drug holidays) are too common to ignore. Drugs should be designed to take this into account so that drug regimens are not designed for the minority who are strictly punctual.

6. Interpretation of trial results in light of adequate compliance measures increases the likelihood that pre-market trials will define the optimal dose, rather than an unnecessarily high dose, as often happens.

7. Prescribers should pay close attention to compliance during the initiation phase of long-term drug treatment for chronic diseases, so as to minimize the risk of over-prescribing to get better drug responses from partially compliant patients.

In general, we have an opportunity to change compliance from a problem to a method for optimizing therapeutics.

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