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Review Article

Patient Compliance: A Milestone in Therapy

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ABSTRACT

Quality healthcare will be obtained by the adherence or the compliant behavior of the patient. Poor compliance has a major effect on the clinical consequences and the therapeutic effects of the dosage regimen. The present review is an effort to study the reported clinical studies and the referred conclusions. Studies show that poor compliance reduces the therapeutic efficacy of the dosage regimen to a certain degree. Poor or partial compliance may be due to several reasons, one of which is the behavioral patterns of the patients. Several studies report the methods to measure compliance so as to determine the effect of the compliance on the therapeutic efficacy. Compliant patients have the greater chances of obtaining the maximum benefits of the prescribed medication.

Keywords: Patient, Compliance, Clinical Trials

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INTRODUCTION

Poor patient compliance to a medication has major impact on the success of patient care, conduct and results of the clinical trials. Reported clinical studies suggest that poor compliance may result in increased possibilities of hospitalization in case of patients with hypertension^[1] and reduced improvements in hypercholesteremic patients,^[2] and increased mortality rate in patients with acute myocardial infarction^[3]. The possible effect of poor compliance includes less knowledge on the therapeutic efficacy of the medication. The enough magnitude of therapeutic effect due to poor compliance may show negative results of the clinical trials, where there are chances of positive response^[4-7].

In other word if the patients have an accurate behavior with the physician or other health care services then he is said to be compliant. Poor compliance may include inattention to diet or workout plans, not having the dose in prescribed manner or having them at improper intervals of time, failure in refilling the prescriptions, irregular follow-up visits to the physician etc. The focus of this review is on compliance to medication regimens.

Patient noncompliance may be due to several reasons. The simplest reason may be the forgetfulness tendency in case of non-symptomatic conditions such as hypertension.

Alternatively, poor compliance may also be due to potential side-effects of the treatment, perception of the patient that the treatment would not cure the illness or personal belief on the health status. For example, a study on the elderly diabetic^[8] patients when evaluated showed positive impact on the health in case of patients compliant to fasting blood sugar treatment when compared to the hospitalized alternates thus stating that an individual's behavior can have a positive impact on the health status. Additional reasons for poor compliance include cost of the medication, reasoning of the patient or the complexity of the dose regimens. The latter two reasons are more common in case of elderly patients resulting in patient noncompliance.

Measuring Compliance

The general method for measuring compliance may include use of biological marker like plasma concentrations, urine assay which provide direct information from the patient. Another method may be counting the pills that give the count of the returned bottles. All these methods can be used for measuring compliance but each of the method has an inadequate effect which may be:

1. Difference in measured compliance when two or more methods are evolved

2. Comparison to newer electronic methods to quantify compliance

The limitations to the pill count method have been reported by several authors. [9, 10]

For example, Pullar^[9] et al assessed compliance by both the plasma concentration and pills count method on 225 subjects. 204 of the subjects showed a follow up visit. Out of which 161 of them showed compliant as their pill count was about 90%-109% indicating that the medication was properly followed. But 51 out of the 161 had doses and body weight plasma concentrations which was completely opposite to the pre-assumed results. Due to the large differences in the results of the two methods, pill count method for measuring compliance cannot be justified. The insufficient assessment of the compliance due to patient interview has been highlighted by reports such as that of Norell^[11], that shows the measurement of compliance by four methods^[12-15] one of which included patient interview and followed by other methods. The results were that the interview rates ranged from 12%-31% as compared to other methods which showed 32%-82%. In another study Caron, reported that most of the patients had taken only 47% of the medication and claimed to have taken 89%.

In recent years the use of microcircuitry which consists of microminiaturized chips for electronic monitoring of the patient compliance which assess the compliance from the date and time on which the medication has been dispensed. They provide the most accurate results. They have been attached to pill bottles, blister packs, aerosol containers etc. They also had an advantage over the traditional measures that overestimated the substantial compliance.

Magnitude and Pattern of Poor Compliance

Some studies reported good compliance rate up to 90%, while some documents often poor patient compliance. Good compliance may be associated with lesser side effects of the medication of acute and symptomatic diseases and with regular diagnoses^[16]. In the Physicians Health Study^[17] good compliance is the indication of the interested and highly educated medication system. However, compliance rate may also be low as up to 50% or less. Given that the traditional methods provide an overstated result of the substantial value, the magnitude of the problem may be inappropriate.

While the number of doses taken may provide the simplest method for determining the compliance however it cannot deliver the real compliance as the pill count may also include doses taken at irregular intervals or during no dose period hence it is apparent that pill count method for measuring the compliance might be inadequate and the magnitude of the problem will not be recognized due to irregular drug taking pattern.

The aspect and characteristic of the irregular dosing can be determined using electronic measuring devices. For example, the compliance tends to better with regular follow-up visits to the physician. Thus, studies by Cramer et al^[18] demonstrated that the compliance percent was 88% during the clinical visit while it was 73% in case of failure to visit the clinic.

On other hand electronic devices helps to assess the compliance during "drug holiday" or the period during which the medication is not taken. Thus, De klerk et al studied the drug taking pattern in 65 subjects with ankylosing spondylitis prescribed with one day medication. While 80% of the doses were taken out of which only 61% were taken during the prescribed episode. Extra doses were

taken on a 3.4% of the day while no dose was taken during 19% of the days monitored. Among the nine subjects with extra dose percent about 81%-90%, four of them showed drug holiday period of 13 days. In Kass et al study of glaucoma in 184 patients prescribed with four in a day pilocarpine eye drops, 24.5% of them showed one day per month no dose period while 52.7% showed five doses per day as the night dose was emitted. Thus, it is evident from the studies that a dose-friendly schedule aided to improve compliance. A potential influence of the irregular drug taking pattern was studied by Cramer et al in patients with epileptic seizures, showed seizure attacks during doses were missed.

Another aspect of drug taking pattern on compliance is that it tends to reduce with time. Thus, in the Physicians Health Study the compliance rates were 95.3% which periodically reduced to 83.8% during the study itself. In the studies of the left ventricular dysfunction the compliance rates were 80% during the first year, 74% during the second and 69% after three years.

Effect of Poor Compliance on Sample Size Requirements in Clinical Trials

When the patients do not comply with the prescribed medication regimen the therapeutic efficacy of the treatment tends to reduce. But in case of clinical trials reduced efficacy will reduce the corresponding in between group differences thus resulting in the increase in the required sample size therefore the magnitude of the potential sample size is enlarged.^[4-7]

To measure the impact of the compliance on the sample size in clinical trials, Schechtman and Gordon^[4] employed both hypothetical and compliance data from Lipid Research Clinics (LRC) Coronary Prevention Trail. The hypothetical data showed that the goal was to compare the success rate in the clinical trial, and the placebo group showed up to 40% success rate and the treatment group showed 60% success rate which have taken the medication in the prescribed manner. A compliant patient is one who takes 80% of his medication and the success rate was found to be 90% in case of patients who took all of their pills. Using the data from the LRC trial it was stated that the cholesterol was reduced only by 32.55% in non-compliant patients and they received only 40% of the therapeutic efficacy when compared to compliant patients. Table 1. Shows the hypothetical data correlating the compliance and the dose size given by the studies of Schechtman and Gordon. Thus, the results indicated that if the compliance rate is 70% then the size requirement is 1.84, if the rate is 60% then the size requirement is 2.14 and 2.52 if the compliance rate is 50%.

Table 1. Effect of Poor Compliance on Sample Size

Percentage of patient who comply	Sample size ratio
90%	1.40
80%	1.59
70%	1.84
60%	2.14
50%	2.52
40%	3.01

In the LRC trail^[2, 25], the treatment group was provided with a six daily packets of cholestyramine, a cholesterol lowering agent and was compared to the placebo group. The primary consequence was coronary heart disease mortality. If the compliance meant at least having five of the six daily packets then the compliance rate of placebo group was found to be

67.3% as compared to the 50.8% of treatment group thus the success rate of the placebo group was found to be 40% and that of the treatment group was found to be 90% as they had taken all the pills. The sample size ratio is the ratio between the required sample size and the corresponding patients who compliant to the sample size.

Effect of Poor Compliance on the Clinical Status of the Patient

Partial or poor compliance might be a hindrance if there is a causative relation between not taking the medication and the clinical status of the patient. On the other hand, it can be instinctively stated that a poor compliance of an effective medication can provide negative results of the clinical status. But at the same time the causative relation is dependent on the specificity of the case like the disease in question, the half life of the drug and the frequency of the medication. Moreover, poor compliance can also be associated to behavior pattern of the patient, hence the degree of negativity of the clinical consequences cannot be figured out, as the behavioral aspect correlates to poor compliance. In the Coronary Drug Project [19], patients compliant to clofibrate a lipid lowering agent, showed lower mortality rate compared to the non-complaint patients. The initial studies show that there is a correlation between the compliance and the mortality rate. But a further look at the study shows the same relation in case of the placebo data, hence the reduced mortality rate in the compliers was not only due to the medication but also that they were engaged in other activities that helped in improving their cardiovascular health.

The note in the prior example is that it is not only poor compliance correlated to the degree of negativity of the clinical status of the patient but it is also dependent on the behavioral pattern of the patient under medication that may give negative clinical outcome. With these limitations we can illustrate the degree to which poor compliance may affect the clinical consequences.

The literature contains a number of other studies that connects poor compliance with negative clinical compliance for example, increased hospitalization [20] in hypertension patients, seizures in epilepsy patients and increased coronary heart disease rate. The magnitude of the negative consequences is highlighted by the Joint National Committee on Evaluation which states that the higher rate of uncontrolled increased blood pressure is due to non-compliance, by a 1984 conference on the therapeutic consequences of non-compliance, which suggested that 125,000 annual death results from non-compliance in patients with cardio vascular disease.

Improving Compliance in Clinical Trials

Since poor compliance has a major affect on the clinical consequences and to the substantial efficacy of the treatment, it is possible that a number of researches are being carried out to enhance the compliance strategies. Such strategies can be broadly classified into two categories:

1. Those that precede the initiation of the study therapy^[2,5,22,24]
2. Those that are implemented after randomization^[2,25]

Compliance enhancing strategies prior to randomization are mainly focused that the patients are more complaint who are being studied. This can be carried out by performing a formal or informal event before randomization. The informal event is carried out as in the LRC trial [21], where the patients

are expected to attend the follow-up visits to the physician to assure that they compliant. If this event fails then it is evident that the patients are more likely to be non-compliant in future. A formal run-in also carried out before randomization which involves the potential patients who were compliant in the informal run-in. It involves placebo medication and the clinical visits. Patients who do not comply are excluded from the trial prior to randomization. It has been established that a run-in strategy has increased the power of the clinical trials. In general, it evident that the run-in strategies have been beneficial when the poor compliance is associated with reduced clinical consequences.

Compliance that involves randomization covers a broad range of activities that are discussed by many investigators [23]. These include educating people about the disease and the compliance, reducing the complexity of the dosing regimen that would be appropriate to the patients schedule, establishing a positive relation between patient and the clinic, financial incentives, self-administered approaches such as proving calendars for remembering when the doses are to be taken, special packing like blister packing with instructions and encouraging the family members for supporting the patient.

Compliance enhancing must be personalized to the patient and to the specific circumstances. Their achievement completely depends upon the inventiveness and the assurance of the health care provider.

CONCLUSION

Poor compliance is associated with both the patient and the medication regimen that may affect the effectiveness of the medication and also the conduct of the clinical trials. The magnitude of the compliance can be measured using electronic devices that provides the accurate results showing the percentage of compliance less than or equal to 50% which is not uncommon. This may help in improving the treatment efficacy and reduce between group differences a situation that may lead to more numbers of clinical trials. Poor compliance also results in severe consequences of the clinical trial which have been demonstrated in several studies that include increased mortality rate, hospitalization rates, reduced control over hypertension, increased seizure attack in epileptic patients, increased rejection rates in transplant patients. Because of these consequences it gives opportunities to the researchers to develop strategies that would enhance the compliance in accordance with the prescribed schedule.

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