

Epidemiology of Adherence and Nonadherence as Indicator of Inappropriate Treatment: “Adherence Useless” And “Nonadherence Adequate”

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Abstract

It is a simplification to accept that all bad clinical control derives from non-adherence. There are data that indicate that there is a high prevalence of therapeutic errors, inadequate treatments, and diagnostic errors, as causes of poor clinical control with good compliance, and on the other hand, there is good clinical control with non-adherence. The prevalence of "useless compliance" (patients who have adherence with the treatment but are not clinically controlled) can vary between 15% -77%, and the prevalence of "appropriate non-adherence" (patients who do not comply with the treatment but are clinically controlled) would be between 7% -63%. It is surprising that these very important figures of prevalence of "useless compliance" and "adequate non-compliance", which indicate diagnostic and therapeutic errors and low medical effectiveness, are not taken into account in epidemiological studies of compliance, so that these data appear to be in "the blind spot" of the researchers that only emphasize the importance of compliance to achieve clinical control, which is at least a partial, simplistic and it "blame the patient." Both clinical and epidemiological studies on therapeutic compliance usually are initiated if disease control is not adequate, but it is essential to verify that the diagnosis and therapeutic indication are correct; Only after this phase should the patient be evaluated about poor compliance. To improve the effectiveness of health care, it must be faced the problem of therapeutic non-compliance by the patient, and diagnostic and therapeutic deficiencies on the part of the doctor.

Keywords: Medication Adherence/statistics & numerical data; Patient Compliance/statistics & numerical data; Drug Therapy; Drug Prescription; Practice-Based Research; Practice Patterns, Physicians'/standards; General Practice

Introduction

Therapeutic compliance has been defined as the degree to which the behavior of a person corresponds with recommendation of the health professional. But, there is no single definition of compliance (synonym: adherence) with which all authors agree. Several terms associated with the concept of adherence to treatment are used: therapeutic alliance, cooperation, compliance, mutuality, collaboration; among others (1, 2). At any case, nonadherence may lead to negative

outcomes and long-term mortality especially among patients with chronic conditions and on complex medication regimens (3, 4).

Nonadherence to chronic medication regimens is common. A large body of research finds that in various settings, from 30-60% of patients with chronic illness (such as hypertension, bronchial asthma, depression, etc.) are non-adherent to treatment and this figure can be considerably higher in developing countries (5-14). So, medication non-adherence is a

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major public health issue and is associated with serious clinical and economic consequences (15).

For example, it has been reported that approximately between 43% to 65.5% patients who fail to adhere to prescribed regimens are hypertensive patients (16). In systemic lupus erythematosus the percentage of patients classified as nonadherent to medication is 75% (17). In terminally ill patients 60% were noncompliant (18). The range of medication nonadherence is reported to be 28-52% for major depressive disorder, 20-50% for bipolar disorder, 20-72% for schizophrenia, and 57% for anxiety disorders. Approximately 40% of patients stop taking their prescribed antipsychotic medication within 1 year and about 75% discontinue their medication within 2 years. Even with depot medication, about 25% of patients stop keeping scheduled appointments and no longer receive depot injections within 1 year after starting treatment (19). At least 50% of patients with asthma or COPD take less than 75% of the prescribed inhaled medication, and only 15% of patients with asthma take the drugs as prescribed for more than 80% of the days (20).

Medication non-adherence is a major impediment to the management of diseases and risk factors. Pharmaceutical treatment is essential to the management of most chronic diseases, but patients' failure to take medications as prescribed often results in failure to meet treatment goals. Medication non-adherence has been associated with a worse evolution, a greater number of relapses and a higher economic cost. Even in the case of diseases where the treatment saves the patient's life, many of them do not comply adequately. Suboptimal adherence can result not only in progression of disease, but in drug resistance, often to multiple classes of drugs. Improving adherence is thus of vital clinical and public health importance, and leads to preventable costs and hospitalizations (21-23).

The treatment of chronic illnesses commonly includes the long-term use of pharmacotherapy. Although these medications are effective in combating disease, their full benefits are often not realized because approximately 50% of

patients do not take their medications as prescribed. Factors contributing to poor medication adherence are myriad and include those that are related to patients (e.g., suboptimal health literacy and lack of involvement in the treatment decision-making process), those that are related to physicians (e.g., prescription of complex drug regimens, communication barriers, ineffective communication of information about adverse effects, and provision of care by multiple physicians), and those that are related to health care systems (eg, office visit time limitations, limited access to care, and lack of health information technology) (24).

Medication adherence research has increased substantially over the past four decades using observational, interventional and implementation research designs. Despite these increased research efforts by many disciplines, progress has been hindered by variability in methodology and poor and/or incomplete reporting of medication adherence research (e.g. inconsistent definitions, inadequate measurement of adherence outcomes, suboptimal analyses, insufficient description of intervention delivery settings, scant theoretical underpinnings) (15).

All of the above being true, but in this clinical-epidemiological framework, however, the reflexive reader of the studies on therapeutic compliance may have a feeling of "cognitive dissonance" (the tension or discomfort that is perceived when we maintain two contradictory or incompatible ideas) (25). When reviewing these studies: there are a certain number of patients, sometimes figures very high, who comply with the treatment imposed by the doctor, but are not controlled clinically, and also surprisingly, there is a non-negligible number of patients who do not are adherent with the treatment but they are controlled clinically. However, these amazing, impressive, unusual, and unforeseen data do not seem to interest the epidemiologist or the clinician.

It can be thought that, as in the dead angles of the vehicles (the "dead angle" is a side area of the vehicle in which the driver has no vision by means of any rearview mirror, neither the interior nor the sides; thus, at the time If you change your lane, it

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is not possible to see the vehicle that circulates in that deadlock, so that there may be serious lateral collisions), the relationship between pharmacological adherence and clinical control of the treated disease, and its counterpart, nonadherence and clinical control, they are two dead angles of the epidemiological vision that are not usually observed, and that nevertheless show important concepts and data about the efficacy and appropriateness of the treatment (or about its lack of efficacy and the inappropriateness of it).

In this scenario, this article, which is a personal view, based on a chosen narrative review and the author's own experience, aims to reflect, conceptualize and synthesize some fundamental elements, which generally fall outside the usual angle of vision of epidemiological elements of the compliance and non-compliance, especially in general medicine, and its clinical and epidemiological applications.

Methods

For the literature review, a pragmatic approach was used that was based on a non-systematic or opportunistic narrative review considered the bibliographic references of selected articles and opportunistic searches on the Internet, in English and Spanish.

Discussion

Definitions and measurements of adherence vary widely; this hinders comparisons being made between studies and populations (26). However, it is clear that approximately 50% of patients stop taking their medications 6 months after drug initiation. Numerous factors contributed to medication nonadherence. Factors associated with the nonadherence are multifaceted. Reasons for nonadherence go beyond simple forgetfulness. Patients' perceptions and beliefs, age, living alone, perception of insufficient social support, limited insight, low therapeutic alliance, presence of symptoms, comorbidity, substance abuse, unemployment, low social functioning, side effects, poverty, lack of family support, perspective of illness and stigma, lack of insight, failure to improve with treatment, long queues when attending

outpatient appointments, various social and cultural myths and beliefs regarding conditions / medicines, the use of alternative medicine, low education, rural residency, childlessness, limited comprehension of medication instructions, dissatisfaction with treatment, as well as drug costs, etc. have been associated with an increased risk of nonadherence (17, 19, 27-29).

Medication Compliance and Medication Persistence Are Two Different Constructs

Medication compliance refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen." Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be defined as "the duration of time from initiation to discontinuation of therapy." No overarching term combines these two distinct constructs (30). Another term used is "discontinuity of pharmacological therapy." By "discontinuity of pharmacological therapy" is meant the interruption of the therapeutic scheme followed by a patient. The discontinuity of the treatment indicates in some way a discontinuity of the doctor-patient relationship. Each type of doctor-patient relationship implies a different relationship with pharmacological treatment; but also, the doctor-drug approach style imposes a doctor-patient relationship (31-33).

Types of Drug Nonadherence

There are several varieties of default. When the method used allows its quantification, it can be considered non-compliance, due to omission or alteration of the dose, when it affects 100 % of the recommendation made, although in general limits of variation are accepted such as considering compliant patients if the treatment is observed above 75% or 80%, or the range of 80-110% of the prescribed dose is admitted (below hypocompliers, above hypercompliers). Normally, this cannot be assessed through interviews or appointment assistance, where the evaluation is strictly qualitative (34).

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Two types of drug nonadherence are usually distinguished: intentional and unintentional. Intentional nonadherence is an active decision by patients who decides not to take medications as prescribed because of beliefs, perceived need or benefit, side effects, or burden of treatment. Unintentional nonadherence is a passive process whereby patients fail to adhere to treatments because of circumstances beyond their control. Individual adherence to the different drugs a patient takes can therefore vary considerably, with various consequences depending on the drug or disease of interest (3).

Adherence can be divided into three interrelated yet distinct phases: initiation, implementation, and persistence. Initiation refers to taking the first dose of a prescribed drug; Initial medication non-adherence has rates between 6 and 28% in primary care (35). Initiation is followed by the implementation phase defined as 'the extent to which a patient's actual dosing corresponds to the prescribed dosing regime from initiation until the last dose is taken'. Discontinuation refers to patients stopping the medication on their own initiative, taking no doses thereafter. Persistence expresses the time between initiation and the last dose. Issues with correct medication taking can occur in any of these three phases, for instance late, incomplete, or non-initiation, suboptimal implementation of the dosing regimen (for example, late, skipped, extra, or reduced doses or drug holidays), or early discontinuation (non-persistence). Each phase creates methodological challenges related to how medication use is operationally defined, measured and analysed (15).

Measurement of Adherence

It has been used several different methods to estimate the adherence of patients to their medications. These methods, which can be used either separately or in combination, include review of medical records, patient self-report, family report, residual pill counting, electronic measurement devices, prescription refill rates, biological markers in serum or urine, assays to quantify

medications or their metabolites, and therapeutic outcome or clinical control (26).

Several approaches have been tried to investigate the medication-taking behavior and the traditional methods such as pill counts, clinical reports, prescription refills and patient-reported measures are some of the cheap and acceptable ones to provide medication adherence information. Several self-reported validated questionnaires have been developed to monitor medication adherence in chronic disease patients, as with hypertension patients. Some of the scales suitable for measuring adherence in chronic disease patients include Morisky medication adherence scale-8 (MMAS-8), Brief Medication Questionnaire by Svarstad et al, the Hill-Bone Compliance scale, and the Adherence scale by Culig et al. Of these, MMAS-8 remains the best known and most widely used scale for investigating medication adherence in chronic disease patients (16). Probably, objective surrogate and direct measures of adherence should be performed as part of a evaluation of diseases difficult to control cynically (36).

Adherence and Non-Control of the Disease and Nonadherence and Control of the Disease

As can be seen from what has been said so far, therapeutic compliance studies must face many methodological and conceptual challenges. But, of course, Nonadherence is one of the most common causes of therapeutic failure in general and specialty clinical practices (37). And Nonadherence to medications is a potential contributing factor to the occurrence of concomitant diseases (16). Despite the difficulties of having valid and homogeneous objective measurements of compliance, and of the impact on health or symptoms, it can be accepted that:

1. In general, compliance is associated with good clinical control of the health problem treated
2. There are a certain number of patients who are classified as adherents to drug treatment being actually non-compliant
3. In general it can be shown that when comparing clinical control between

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compliers and non-compliers, this will be better in the former.

4. Clinical changes in the patient's health most clearly are related to acuteness of symptoms at presentation than with therapeutic compliance (38).

5. The clinical results should expand beyond the symptoms, and include functional status and well-being defined from the patient's perspective (39).

6. Although patients tend to overestimate their adherence, when they acknowledge their non-compliance, it is almost always true (40).

7. Declared self-compliance techniques have low rates of sensitivity and specificity, but have clinical utility to identify non-compliant patients (41).

8. The self-reported compliance underestimates the non-compliant, but this can be overestimated by other methods of assessment (Morisky-Green test, knowledge of the disease, medical judgment, attendance at appointments, and degree of control of organic variables such as BP). But, methods of degree of control of biological variables, medical judgment and compliance self-communication have good validity and concordance to identify the non-compliant (42-44).

9. Objective surrogate and direct measures of adherence should be performed both as part of assessment of a disease with difficult clinical control, and are important before prescribing expensive or novel therapies (36).

Not all drugs patients take have the same impact on their health outcomes: some are intended to prevent complications, others to reduce symptoms. The objective value of "clinical control" (impact on health or symptoms) can be evaluated more easily in situations in which it is possible to obtain a quantitative variable; A paradigmatic case is arterial hypertension, where the blood pressure (BP) figure can be obtained (despite being a continuous variable and subject to multiple measurement biases) as an indicator of "clinical control" (and in fact, this is how doctor acts in the clinic). But also, that clinical control can be measured in diabetes (based on the HbA1c figure),

dyslipidemias (based on the LDL cholesterol figure, for example), etc.

Therefore, if it is accepted that therapeutic compliance is associated with clinical control, the percentage of patients with good therapeutic compliance and poor clinical control is an indicator of inadequate treatment (type of drug, dose, pharmacological interactions, etc.). So, patients may develop tolerance to the effect of drugs and require higher doses to achieve the same clinical effect; drug-drug interactions may exist; some drugs reduce the absorption of essential nutrients from food, which could lead to nutritional deficiencies; wrong drugs may be prescribed, for example when a patient receives medications that do not treat the patient's condition; drugs may be prescribed at doses too low, and the patient receive doses that are not strong enough to obtain beneficial or therapeutic effects; doses too high may be prescribed, and thus cause harmful effects; with inappropriate frequencies; with inappropriate duration; or simply that that drug is not necessary. In all those situations it is a "useless adherence."

On the other hand, the percentage of non-compliant patients who nevertheless have good clinical control also represent another indicator of poor treatment; in these cases, it would be a "proper" or "wise" non-compliance by the patient in the face of an inappropriate pharmacological treatment by the doctor (for example, by incorrect diagnosis of the health problem, unnecessary pharmacological therapy, there is no medical indication for drug treatment, therapy duplicate, etc.).

For example, in the field of hypertension, it is admitted that hypertension is a global challenge which accounts for high morbidity and mortality rates in the world. It is often admitted as an indisputable fact that the availability of effective anti-hypertensive medications does not result in a good outcome in controlling blood pressure which points towards poor adherence (45).

But, some pioneering study, in the field of compliance with treatment in arterial hypertension already indicated that the prevalence of "useless compliance" is 50 % (only 50% of hypertensive patients

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who comply with the treatment show controlled BP figures). And the prevalence of "adequate non-compliance" can be 7% (in this field of hypertension, 7% of non-compliant hypertensive patients have controlled BP figures) (46).

Other studies have reported that the coincidence rates between compliance and control of hypertension are only 23% of cases (47), which represents 77% of "useless compliance". Other studies repeatedly report that nonadherence to antihypertensive medications was noticed in 45% -50% of the patients, and a higher proportion of uncontrolled BP (85%) was in patients nonadherent to medication. In this way, there are 15% of uncontrolled BP patients but with adherence to antihypertensive medications. In the same line, it has been communicated that, consequently, because of nonadherence, most (nearly 3-quarters; 75%) of the hypertensive patients do not achieve optimal BP control. That is, there could be up 25% of patients with nonadherence to antihypertensive medications, but with controlled BP ("adequate non-compliance") (16).

Other studies that indicate that pharmacological non-compliance is a fundamental cause of poor clinical control of hypertension and diabetes (but less important in the case of dyslipidemia), also point out, but without paying attention, that only 50% of hypertensive patients with Good compliance are controlled, only 82% of diabetics with good compliance, and only 75% of dyslipidemic patients. And 87% of hypertensive patients with poor compliance have poor BP control, 78% of diabetics with poor compliance have poor HbA1c control, and 37% of dyslipidemic patients with poor compliance have poor control of LDL cholesterol figure (48). That is, there is a prevalence of "useless compliance" of 50% in hypertension, 18% in diabetics, and 25% in dyslipidemic patients. And there is a prevalence of "adequate non-compliance" of 13 % for hypertension, 22% in diabetes, and 63% of dyslipidemic patients.

Along the same lines, it was reported that in asthmatic patients who were non-compliant (compliance was measured using the Turbuhaler Inhalation Computer, which recorded the time and date of each inhalation over a 12 week

period) made little use of the "rescue" salbutamol, and comparing compliance among patients with an inhaled corticosteroid (budesonide), a short-acting inhaled beta-agonist (terbutaline sulphate) and a Turbuhaler inhaler containing a combination of the two drugs, respiratory function tests were similar in both drug groups, and did not change throughout the study (20).

In this regard, attention has been drawn to the fact that the results of the studies contradict the widespread belief that factors related to non-compliance are primarily responsible for treatment-resistant hypertension: Non-compliance with treatment was not more prevalent in patients with treatment for resistant hypertension than in treatment responsive patients. Factors other than patients' compliance with treatment regimens should be examined to explain lack of response to antihypertensive drugs (49).

Often the terms efficacy and effectiveness can take numerous meanings depending on the area in which they are applied (medicine, management, engineering, etc.), but effectiveness refers to objectives / results relationship under real conditions, and efficacy refers to objectives / results relationship under ideal conditions (50).

In this way, it can be thought that the clinical outcome of a drug in laboratory studies or even in clinical trials indicates the efficacy of that drug; but in real life, "useless compliance" (complying with the treatment imposed without achieving clinical control) measures a negative aspect of the effectiveness of a pharmacological treatment (of its non-effectiveness: between 15-50% of pharmacological treatments in real life may be non-effective; or in other words, the real-life effectiveness of a drug treatment may not be as greater than 50-75%, although the efficacy of that drug in the laboratory is 100%).

Therefore, sometimes the drug may not work, but probably more frequently it is the treatment that does not work because it is not used correctly. For example, regarding the lack of clinical control in hypertension despite good compliance, we must consider factors such as: correctly knowing the therapeutic indications and the specific

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situation of each patient, stratifying their risk, avoiding the use of associations of non-beneficial drugs for better BP control, etc. (14). Even the good compliant patient can get to cumulate medications and take "only the medicines prescribed by doctors", but unfortunately they can be the same or antagonistic drugs prescribed by different uncoordinated doctors, so that "compliance" implies much more doses high or low of adequate.

And on the other hand, the "adequate non-compliance" (not complying with the treatment and maintaining good clinical control, which can be, at least, between 7-25%) measures a negative aspect of the effectiveness of the medical professional: although it can be admitted that the efficacy of the doctor (the objectives / results ratio under ideal conditions; perhaps an exam or other type of academic test) is 100%, its effectiveness in real life conditions can be between 75%-93%; In other words, the most efficacy doctor possible will have a real lack of effectiveness between 7-25%. This situation of difference between the efficacy and effectiveness of a drug / treatment has been seen frequently in epidemiological studies (51).

Conclusion

There are other possible meanings with important clinical and epidemiological implications of the usual sense of the concept of therapeutic adherence /

compliance, for which clinical doctors and epidemiologists are often blind.

It is a simplification to accept that all more clinical control derives from non-compliance. There are data that indicate that there is a high prevalence of therapeutic errors, inadequate treatments, and diagnostic errors, as causes of poor clinical control with good compliance (useless compliance), and good clinical control with noncompliance (adequate non-compliance).

The prevalence of "useless compliance" (patients who are adherent with the treatment but are not clinically controlled) can vary between 15% -77%, and the prevalence of "appropriate non-compliance" (patients who are not adherent with the treatment but are clinically controlled) it would be between 7% -63% (**FIGURE 1**). It is surprising that these very important figures of prevalence of useless compliance and adequate non-compliance, which indicate diagnostic and therapeutic errors and low medical effectiveness, are not taken into account in epidemiological studies of compliance, so that these data appear to be in "the blind spot" of the researchers and only emphasize the importance of compliance to achieve clinical control, which is at least a partial, simplistic and "blame the patient" as it ignores the dependent factors of the doctor to achieve clinical control, while looking only at the patient's compliance factors.

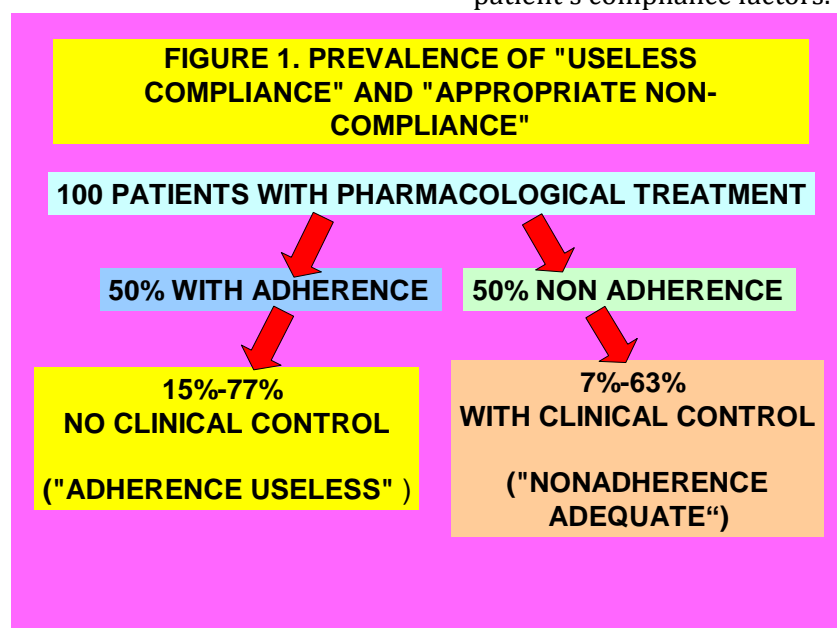


FIGURE 1: Prevalence of "Useless Compliance" And "Appropriate Non-Compliance"

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Clinical and epidemiological studies on therapeutic compliance always stress that "patients tend not to comply," but surprisingly they do not realize that their data also suggests that "doctors tend not to comply." To improve the effectiveness of healthcare it should be face the problem of therapeutic non-compliance by the patient, and the diagnostic and therapeutic deficiencies on the part of the professional.

Both clinical and epidemiological studies on therapeutic compliance are usually initiated if disease control is not adequate, but it is essential to verify that the diagnosis and therapeutic indication are correct; only after this phase should the patient be evaluated as a poor compliance patient. It is necessary to investigate these "dead angles" of compliance and clinical control more deeply and apply the results to clinical practice.

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