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Narrative Review

The Benefits and Risks of Adherence to Medical Therapy

Anthony R. Scialli, MD[1], Keene Saavedra, PharmD[2], Adriane Fugh-Berman, MD[3] [a]

[1] Department of Pharmacology and Physiology, Georgetown University Medical Center, Washington D.C.; Obstetrics and Gynecology, Georgetown University Medical Center, Washington D.C., [2] Department of Pharmacy, Grand Strand Medical Center, Myrtle Beach, S.C., [3] Department of Pharmacology and Physiology, Georgetown University Medical Center, Washington, D.C.

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Noncompliance or nonadherence to prescribed medication is common. Reasons given by patients for not taking medications as prescribed include cost, adverse effects, or perceived lack of effectiveness, all of which are important factors in shared decision-making between health care providers and patients. It has been assumed that better compliance with medication therapy would mean better control of disease, prevention of disease-associated health impairment, and cost savings, but these assumptions are questionable. Although adherence to some medications, including anti-tuberculosis drugs and oral contraception, is necessary for effectiveness, it is unclear whether adherence to many other medications improves outcomes. Patients who adhere to almost any medication, including placebo, have better health outcomes, but these benefits could be due to healthy behaviors for which adherence is a marker. On the other hand, compliance with treatments that are harmful increase harms. Efforts to increase compliance with new drugs may be risky because newer drugs have limited safety data. We recommend that practitioners use noncompliance as an opportunity to address problems identified by the patient, including medication cost, side effects, and lack of perceived benefits. We also argue that inadequate attention has been paid to the possible role of drug manufacturers in distorting information about the causes, benefits, and harms of adherence.

INTRODUCTION

It seems intuitive to most prescribers that adherence to medical therapy is desirable. For patients, the issue is more complex. Certainly, in some cases, adherence has clear benefits. For example, directly observed antimicrobial treatment for latent tuberculosis results in better health outcomes for the individual and the community.[1] Using oral contraceptives perfectly results in a 0.3% pregnancy rate over the first year, while inconsistent use results in a 9% pregnancy rate.[2,3] In other cases, however, it is not at all clear that strict adherence to all medications has a net benefit either for individuals or populations.

We set out to examine the extant literature on adherence and compliance to medication in an effort to better understand the pharmaceutical industry's role in framing lack of adherence as a public health problem. This paper utilizes a narrative approach, juxtaposing medical, public health and marketing literature in order to draw attention to under-explored issues, including factors affecting medication reluctance among patients in Western countries, the risk/benefit ratio of not taking medications as directed, and the interests of the industry in influencing perceptions of "noncompliance."

The term adherence is sometimes recommended over compliance as it is considered less pejorative; that is, a noncompliant patient may be characterized as uncooperative or misinformed, whereas a nonadherent patient might have legitimate reasons for departing from the recommendations of a health care provider. Advocates for the term adherence argue that compliance implies "passivity and potential lack of patient agreement."[4] The distinction assumes that patients who adhere to a prescription have made an informed decision to take the medication. However, neither the acceptance nor filling of a prescription is equivalent to an informed decision, and the decision to initiate or continue taking medication may also change over time. For this reason, we use the terms compliance and adherence interchangeably to refer to the proportion of prescribed pills taken in a given time. In this choice to consider the terms as synonymous, we follow Cramer et al.[5] who in turn followed Benner et al.[6] It bears noting that the pharmaceutical industry usually uses the term adherence to refer to medication use, and compliance to refer to legal or regulatory issues.

PREVALENCE OF NONCOMPLIANCE

Noncompliance is widespread amongst patients facing a variety of health concerns. In one medical record/prescription

a Corresponding Author: ajf29@georgetown.edu

data base study, 40% of new prescriptions were not filled within a week and one-third of new prescriptions were not filled within a month.[7] Another analysis of 195,930 prescriptions in an e-prescribing database found that only 72% of new prescriptions were filled; adherence was particularly low for newly prescribed medications for hypertension (28.4%), hyperlipidemia (28.2%), and diabetes (31.4%).[8] About 31% of a Brazilian sample was assessed as poorly adherent to medication therapy for chronic, noninfectious diseases.[9] A review of publications from the 1980s until 2006 reported that nonfulfillment rates for an initial medication prescription ranged from 0.5% to 57%.[10] An industry report on claims-based studies of adherence found that adherence ranged from 7% for certain asthma medications to 87% for certain cancer therapies.[11] Among Medicare patients prescribed endocrine therapy for breast cancer, 77% were taking the medication after one year, and 64% were taking the medication two years after the initial prescription.[12]

Evidence suggests that medications intended to prevent rather than to treat disease may result in even less compliance. Only 60% of women with rheumatoid arthritis filled at least 80% of their prescriptions for oral bisphosphonates to prevent osteoporosis after one year, and only one-third of patients were still on medication at the end of three years.[13] For epilepsy, an illness with adverse consequences for under-treatment, a study of Medicare claims showed that among older Americans, one-third of patients had antiepileptic coverage for fewer than 80% of their days.[14] In another study, about half of kidney transplant recipients did not comply with immunosuppressant medication in the absence of reminders.[15]

Up to one-third of patients with a new prescription for diabetes medication did not fill the prescription or filled it only once.[16] Among patients at Kaiser Permanente Northern California who were prescribed statins, those who initiated treatment were more likely to have a diagnosis of ischemic heart disease, prior ischemic stroke, transient ischemic attack, peripheral artery disease, or heart failure.[17] Although 84% of patients were still receiving statins one year after their initial prescription, only 43% of patients had received continuous statin therapy at one year, and 30% had received continuous statin therapy at two years. One year after ischemic stroke, 43% of survivors were adherent to statin therapy.[18] For antihypertensive therapies, 45% of patients were noncompliant; among patients with comorbidities, 31% were not compliant.[19] In a German sample, persistence in use of antihypertensive medication after four years was about 40%.[20]

We have also found evidence that patients may not accurately report their medication use. About half of the patients in a study at the Cleveland Clinic reported that they had complied with medication instructions, but researchers found that the concentration of medication in their blood was not consistent with correct use.[21] Although this study acknowledged the short half-life of some drugs and genetic differences in drug metabolism as possible causes for discrepancies, the authors suggested that there can be a considerable difference between what patients say they take and what they actually take. Based on urine and serum measurements, at least one antihypertensive medication/metabolite was absent in 42% of UK patients and 31.5% of Czech patients.[22] Evidence was lacking for use of any medications in 14.5% of the UK patients and 12% of the Czech patients. Predictors of noncompliance included the number of prescribed medications, age, female sex, and the presence of a diuretic among the prescribed medications.[23] Noncompliance is found across diverse populations and in diverse clinical scenarios, and it is important to explore the reasons for this behavior, as well as possible consequences.

WHY ARE PATIENTS NONCOMPLIANT?

Health care providers may view patient adherence with medication regimens as self-care and may view failure to comply with therapy as self-harm. However, research shows that most patients are not intent on self-harm. In fact, lack of adherence to therapy can be a result of a rational risk–benefit assessment that considers a complex array of factors.

Although reasons for noncompliance are multifactorial, common themes include cost, side effects, lack of perceived need for the medication, and unintentional noncompliance. In a review of 79 studies published between 1980 and 2006, reasons given by patients for not filling a prescription included concern about side effects, concern about taking too many medications, lack of perceived need for the medication, lack of confidence that the medication would be helpful, and cost.[10] A review article on factors associated with noncompliance in the elderly identified patient factors (e.g., depression, low cognitive function, poor memory, ethnicity, beliefs about medication), medication factors (e.g., packaging, multiple prescriptions, cost, side effects), physician factors (e.g., poor communication), system factors (e.g., lack of patient education or follow-up), and other factors (e.g., lack of caregiver) as contributors to medication noncompliance.[24] One study found that not filling diabetes medications was associated with depression.[25] Another found that, among African-Americans, mistrust of the health care system or health care providers was an important potential contributor to noncompliance.[26]

COST

Medication cost as a reason for noncompliance was addressed in a survey of more than 22,000 patients 55 or older in 11 high-income countries.[27] Cost-related nonadherence to therapy was reported in almost 17% of respondents in the U.S. The lowest reporting rates for this source of noncompliance (0.7–3.6%) were in France, Norway, Sweden, Switzerland, and the United Kingdom. Cost-related nonadherence was associated with patient age, poverty, and lack of available pharmacy coverage.

A New Zealand study used structured interviews to explore reasons for medication noncompliance among people living in poverty.[28] In New Zealand, most medications are covered by the government with a per-item charge to the patient of NZ $5 (US $3.50). Patients reported prioritizing which medications they paid for; for example, picking up only mental health medications, but not other medications, or picking up medications for children, while leaving medications for adults. Other strategies for affording medica-

tions included eating less food, eating less often, choosing cheaper food, and taking medication less frequently than prescribed in order to make a prescription last longer.

Being African-American and living in a rural area were associated with lower compliance with adjuvant endocrine medication for breast cancer.[29] In this study, compliance was higher among those women who received a low-income subsidy that decreased their out-of-pocket medication costs. Lower socioeconomic status was also identified as the mediator of racial disparities in endocrine therapy compliance in another study.[30] Out-of-pocket medication cost reduced compliance with medication for leukemia in Medicare beneficiaries.[31] It is not only elders who are affected; out-of-pocket expenses also reduced compliance among adolescents and young adults with cancer.[20,32]

SIDE EFFECTS

Among Africans receiving antiretrovirals, one study revealed how prior experience affected perceptions of medication side effects. Patients who felt sick prior to therapy were able to tolerate side effects better than patients who felt well, indicating that those already experiencing symptoms were more willing to withstand different symptoms associated with possible benefit of the medication.[33] A Swedish study found that patients made conscious decisions not to comply with antihypertensive medication, primarily to minimize side effects.[34] Among schizophrenic patients using antipsychotics, one study found that 86% experienced at least one side effect, and only 43% reported complete adherence.[35] Feeling worse after taking a medication than before is clearly a disincentive to compliance.

PATIENT CULTURE AND BELIEFS

Perceived lack of effect also hinders compliance. In one study of patients with type II diabetes, only 28% of patients believed that taking antidiabetic medication could reduce the risk of diabetes complications.[36] Nonadherence was inversely associated with the belief that the patient was susceptible to complications of diabetes and the belief that the medication offered a benefit.

We also recognize that patient culture can affect compliance. One review of cultural issues in medication compliance noted that adherence rates are lower among people of color and people of lower socioeconomic status.[37] Some, but not all, studies found that the use of complementary and alternative medicine was associated with lower compliance in some communities of color.[37] Perceived discrimination by the healthcare system also decreased compliance.

FORGETTING

Interviews with patients who exhibited so-called unintentional noncompliance, including those who forgot medication doses, suggested that forgetting medication was associated with lower perceived need for the medication, cost concerns, and concerns about adverse effects of the medication.[38] Unintentional noncompliance in a prospective study of independently living elders showed that a person aged 65–69 had a 10% chance of developing difficulties in managing medications (and more than a 20% chance of developing difficulties in managing finances) within 10 years.[39]

Although memory lapses are sometimes cited as the most important reason for noncompliance, memory-assisting devices may not be helpful.[38,40] A randomized trial of memory-assisting devices showed no benefit in compliance compared to a control group; however, all groups, including the control, showed improvement.[41] A review of 43 studies of memory-assisting devices showed variable results ranging from no effect to as much as a 33% increase in compliance.[42] Another review of compliance-enhancing strategies, including memory assistance devices, reported a combined adherence in intervention groups of 74.3% compared to a control adherence of 60.2%.[43] In these studies, improved compliance decreased over time. In sum, it makes sense that memory lapses affect compliance, but it is unclear whether memory-assist devices are helpful for this problem.

In an attempt to address patient confusion or lack of knowledge, an Australian study assigned medical students to meet with inpatients prior to discharge to go over their medications and the reasons for which they were prescribed.[44] The students wrote down a daily medication schedule for patients to follow at home. Compliance, which was assessed one month later, had improved from 60.3% to 76.3%. More research about the effect of individualized drug education on appropriate use of drugs is needed.

DOES COMPLIANCE IMPROVE HEALTH, OR ARE HEALTHY PEOPLE COMPLIANT?

Health care providers often assume that better compliance with medication therapy means better control of disease, prevention of disease-associated health impairment, and cost savings. However, studies that claim to support these beliefs may extrapolate benefits from changes in surrogate outcomes rather than clinical endpoints, or patient-oriented outcomes.

Surrogate endpoints include, for example, blood glucose levels, cholesterol levels, hypertension, and bone mineral density. Clinical endpoints include death, heart attack, stroke, or bone fracture. Surrogate outcomes do not always correlate with clinical outcomes. For example, lidocaine suppresses arrhythmias following acute myocardial infarction, but increases mortality, and sodium fluoride increases bone density but does not reduce fracture rate.[45] Similarly, reductions in serum lipid concentrations, glucose levels, or lower blood pressure readings may not translate to lower risks of cardiovascular disease, disability, or death.

Therefore, studies that correlate compliance with medication with beneficial outcomes based on surrogate endpoints may have no relevance to clinical outcomes such as prevention of death, heart attack, or kidney failure. For instance, the American Diabetes Association (ADA) recommends a glycosylated hemoglobin (HbA1c) target of <7.0%,[46] although the organization allows that individualization may be appropriate. However, HbA1c is a surrogate endpoint, and it may not predict clinical endpoints, such as mortality. In a retrospective analysis of survival as a function of HbA1c, the lowest all-cause mortality was seen

at concentrations of 7.0–9.5% among patients older than 50 who were treated with metformin plus sulfonylureas for type 2 diabetes mellitus.[47] In patients treated with insulin, all-cause mortality was lowest at HbA1c concentrations of 7.5–9.0%; mortality increased at concentrations both above and below this range. Progression to large-vessel disease followed a similar pattern. Therefore, compliance with medication (especially if insulin is used) to keep glycosylated hemoglobin <7.0% may result in more deaths than a more relaxed standard.

These findings accord with those of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which type 2 diabetics were randomized to intensive therapy or standard therapy.[48] The intensive therapy group successfully reached HbA1c concentrations of 6.4–7.5% but showed no advantage over the standard therapy group in a composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. In fact, all-cause mortality was increased in the intensive therapy group (HR 1.22, 95% CI 1.01–1.46) at the time the trial was stopped, after a mean 3.5 years of follow-up. Similarly, there was no difference in all-cause or cardiovascular mortality in the Action in Diabetes and Vascular Disease (ADVANCE) study between subjects randomized to intensive control (mean glycosylated hemoglobin 6.5%) or standard therapy (mean glycosylated hemoglobin 7.3%).[49] Intensive therapy in the ADVANCE study was associated with a reduction in nephropathy, but not in retinopathy. These studies illustrate how compliance to medication does not necessarily result in better health outcomes for patients.

Hospitalization is particularly problematic as a surrogate compliance outcome in clinical trials because the reasons for hospitalization may not directly relate to compliance. For instance, diabetic patients who do not adhere to medication or diet regimens may be hospitalized more often than compliant patients; however, the decision to hospitalize a patient could reflect clinician concern about an unrelated condition; concurrent hyperglycemia may be incidental. Specifying diagnostic codes has been proposed to improve the use of hospitalization as an outcome. In one study of oral hypoglycemic medication compliance, the researchers used the outcome of inpatient admission with a primary diagnostic code related to diabetes or cardiovascular/cerebrovascular causes in order to show a direct relationship to medication compliance.[50] This strategy still may be susceptible to confounding if the chance of hospitalization for the same diagnosis was influenced by a patient's glycosylated hemoglobin or blood glucose concentrations.

Patients who take medication as directed may be different than noncompliant patients. A 2002 meta-analysis of 63 clinical trials concluded that among patients who did not comply with therapy (medication, diet, or exercise), there were 26% fewer patients with good outcomes.[51] The meta-analysis included type 1 and type 2 diabetes studies using glycosylated hemoglobin or fasting blood sugar as endpoints; coronary artery disease studies using plasma phospholipid concentrations as endpoints; hyperlipidemia studies using plasma lipids as endpoints; and antihypertensive studies using blood pressure as an endpoint. A more recent study of medication compliance found that diabetic patients with medication fills covering at least 80% of their days had fewer all-cause hospitalizations and all-cause deaths than patients with less than 80% coverage.[52] All-cause hospitalizations were recorded in 23.2% of noncompliant compared to 19.2% of compliant patients, and all-cause deaths occurred in 5.9% of noncompliant compared to 4.0% of compliant patients.

Although these studies seem to support the importance of compliance in achieving good therapeutic outcomes, including decreased mortality, there is an alternative explanation. The authors of the recent meta-analysis note that indices of glycemic and lipid control were not correlated with compliance and suggest that patients who comply with medications may also adopt healthier lifestyles.[52] In other words, those who comply with prescribed therapy may also have adopted healthy behaviors, and better health outcomes may be due not to increased medication intake but rather a commitment to responsible choices in diet, exercise, alcohol use, seatbelt use, etc.

This phenomenon has been called the "healthy adherer" effect. The effect was first demonstrated in 1980, when the Coronary Drug Project found no advantage of clofibrate or other medications over placebo. An additional analysis showed that those who complied with the clofibrate regimen showed higher survival rates than those who were noncompliant. There was a similar survival advantage for compliance with placebo.[53]

The healthy adherer effect has since been demonstrated in other studies. For instance, The Women's Health Initiative, which randomized menopausal women to hormone therapy or placebo, found a decrease in placebo-adherent subjects in all-cause mortality, coronary heart disease mortality, cancer death, and hip fracture. The protective effect of placebo adherence persisted after adjustment to use of aspirin, fracture medication, and other medications. Another analysis of 800 baseline risk factors in the subjects could not explain the placebo compliance benefit.[54]

A review of 21 trials on medication compliance in coronary artery disease and congestive heart failure identified three studies in which adherence to placebo was also associated with a reduction in adverse outcomes.[55] A 2006 meta-analysis identified eight placebo-controlled clinical trials in which compliance with therapy and mortality could be assessed.[56] In this analysis, adherence to placebo was associated with a 44% reduction in mortality. In a subgroup of studies on treatment after myocardial infarction, adherence to placebo was associated with a 55% reduction in mortality.

Several other studies show health advantages of adherence to placebo; these include but are not limited to: a study of beta-blockers after myocardial infarction in men[57] and in women,[58] aspirin for preventing death in healthy men,[59] amiodarone for preventing death in myocardial infarction patients with premature ventricular contractions,[60] and candesartan for the treatment of congestive heart failure.[61] The beneficial effects of adherence to placebo may even be dose-related. In the Studies of Left Ventricular Dysfunction (SOLVD) trials, subjects who took at least 75% of placebo pills experienced about half the mortality rate than subjects who took less than 75% of the placebo.[62] A similar decrease in all-cause mortality associated with compliance with placebo was seen in a trial of a

beta blocker in patients with congestive heart failure.[63]

ADHERENCE-ASSOCIATED HARMS

It is worth noting that compliance with treatments that are harmful increases harms. For instance, a meta-analysis of drug trials concluded that mortality was increased in patients complying with therapy to suppress cardiac arrhythmias, with a summary odds ratio for mortality in good compliers of 2.90, 95% confidence interval 1.04–8.11.[56] In other words, compliance to this harmful treatment was associated with almost a threefold increase in mortality.

In another study, the treatment of diabetes mellitus with tolbutamide showed no advantage over the placebo; moreover, among patients who received all their medication for at least 75% of follow-up periods, cardiovascular mortality was lower in the placebo group (3.5%) compared to the tolbutamide group (14.6%).[64] All-cause mortality was 7.7% in the placebo group and 17.2% in the tolbutamide group. These mortality results were not primary outcomes of the study, but by our analysis, the differences between adherence to placebo and tolbutamide are statistically significant ($P<0.05$; Fisher exact test). Based on these worrisome outcomes, we suggest that more attention needs to be given to possible adverse effects of medication compliance.

Adherence to new drugs may cause more adverse effects than adherence to old drugs. An evaluation of adverse drug reaction reports to the US Food and Drug Administration showed more reports, including reports of drug-associated death, for novel drugs than for older drugs, even when adjusted for the condition being treated.[65] The likelihood of a drug acquiring a new black box warning or being withdrawn from the market is 20% over the first 20 years of marketing; half of drug withdrawals occur within the first two years of marketing.[66] Adverse drug reactions are an invitation to noncompliance that may be avoidable by prescription of better established medications.

INDUSTRY'S INTEREST IN NONADHERENCE

Industry's interest in adherence can sometime overlap with medical and public health interests; for example, adherence to an anti-tuberculosis drug regimen should decrease multi-drug- resistant TB.[67] A vaccine regimen against SARS-CoV-2 is expected to decrease individual susceptibility to Covid-19, decrease hospitalizations and deaths, and enhance herd immunity.

However, the drive for profit predominately influences industry interest in affecting provider and patient perceptions of the importance of adherence. Pharmaceutical manufacturers, distributors, and pharmacy benefit managers view patient nonadherence as a marketing problem because patients who decline to fill or refill prescriptions decrease profits. One industry publication characterized nonadherence as "a huge problem for the pharmaceutical industry and all parties with ties to the healthcare system… Adherence has been a pain point for the pharmaceutical industry for decades."[68] Another industry article found that nonadherence results in a $637 billion annual loss in pharmaceutical industry revenue annually, with a $250 billion loss in revenue in the US alone.[69]

A consulting company report encouraged industry attention to adherence, arguing that "with blockbuster expiries, drying pipelines and increasing cost-containment by payers, bridging the adherence gap is a 'must do' for pharmaceutical companies to protect their top line while transforming themselves from product to patient-centric organizations."[70] The report estimated that noncompliance resulted in an average sales loss of 36% per drug product.

Another industry article states that "medication adherence is pharma's new golden goose."[71] The article notes that an analysis of 21 large-pharmaceutical companies by Credit Suisse analysts found that adherence could potentially increase revenues up to 21% and urged companies to hire a "chief adherence officer."

To address patient skepticism about benefits, an industry article recommended more engagement by prescribers and pharmacists in patient education.[68] To address cost, the article briefly mentioned discount cards, but cautioned manufacturers that discount programs are expensive and might not be justified—except for the most profitable of products.

DISCUSSION AND RECOMMENDATIONS

In this article, we have demonstrated that many of the reasons for which patients are not compliant are perfectly rational: the drug costs too much, doesn't seem to be working, or causes adverse effects. Lack of compliance with medication often indicates patient concerns about cost, side effects, or skepticism about the benefits claimed by the prescriber. Any of these are excellent reasons for patients to consult their health care provider to discuss alternative medications, dose reductions, or nonpharmacological options. Thus, patient noncompliance is not evidence of ignorance, laziness, or hostility. Rather than taking offense, the healthcare provider should learn more about a patient's goals and concerns and offer to change the recommended therapy in an effort to meet the needs of the patient. Most importantly, patients are partners, not adversaries, in the healthcare encounter; shared decision-making means that the prescription of medication is elected by the patient after he or she learns about the risks and benefits of the proposed treatment, and alternative treatments.

We consider financial cost as a risk of harm in therapeutic decision-making,[72] and adherence to an unnecessarily expensive medication causes financial harm to both patients and payers. There is always uncertainty about the possible harms of novel, relatively untested medications and newer drugs are often the most expensive drugs. These considerations should guide prescribers toward older, generic medications, which decrease costs and improve compliance.[73–75] For mild conditions, such as marginally elevated blood pressure, research shows that positive health outcomes may be achievable through lifestyle changes,[76] including diet[77] and exercise.[78] Really listening to the patient's concerns and working with the patient is key to excellent health care.

CONCLUSION

Much of the research on compliance has focused on patient behavior, thereby placing much of the responsibility on patients. However, it is clear that practitioners and patients have different risk-benefit analyses. We argue that instead of relegating noncompliance to a patient problem, therefore implying that correcting patient behavior is the solution, nonadherence should be seen as a message to providers that they need to improve treatment options and approaches. Moreover, inadequate attention has been paid to the possible role of drug manufacturers in distorting information about the harms of adherence, and in casting nonadherent patients as irresponsible or careless. Rather than attempting to force compliance with mediocre, but expensive drugs, perhaps we must redirect attention to hold manufacturers accountable for misinforming health care providers about the causes and consequences of noncompliance.

DISCLOSURES

Tony Scialli and Keene Saavedra have no relevant conflicts of interest. Adriane Fugh-Berman directs PharmedOut, a research and education project at Georgetown University Medical Center. She is a paid expert witness at the request of plaintiffs in litigation regarding pharmaceutical marketing practices. No funding was received for this review.

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