



A Study of Adherence to Antibiotic Treatment in Ambulatory Respiratory Infections

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Abstract

Background: Compliance to the prescribed antibiotic treatment is a challenging issue in real world setting. The relationship between healthcare providers and patients is an important factor for compliance. The author conducted a prospective study to assess the adherence to antibiotic treatment in ambulatory respiratory infections.

Materials and Methods: A prospective observational study was conducted in five general medicine outpatient clinics from June 2017 to March 2018 in Hyderabad, India. The patients with uncomplicated, suspected acute bacterial pharyngitis and lower respiratory tract infections were included in the study. The data was processed through Power View program v. 1.3.2. (Aardex Ltd.).

Result: Out of total 60 patients enrolled, 26 patients answered the self-reported adherence question (good self-reported adherence) negatively (59.3%), while remaining patients answered either affirmatively or elicited an unclear response. During the study, 13 patients (30.4%) achieved 80% of all the adherence outcomes (excellent), 5 patients (12.4%) missed only one dose for achieving excellent adherence, 13 patients (28.7%) presented declining adherence over time. Excellent adherence was significantly associated with the number of daily doses of the antibiotic (odds ratio (OR) 0.22, 95% confidence interval (CI) 0.15–0.32) and antibiotic duration (OR 0.77, 95% CI 0.61–0.96). This study compared self-reporting with objectively measured medication adherence using an evidence-based cut-off point in the same study population.

Conclusion: Approximately one in four patients presented with non-adherence to correct dosing and approximately one in four presented with declining adherence over time. The adherence outcomes were consistently and significantly worse with three times-daily antibiotic schedules and better with once-daily antibiotic regimens.

Keywords: Adherence, antibiotic treatment, observational, acute bacterial pharyngitis, lower respiratory tract infections.

Introduction

In medicine, compliance (also adherence, capacitane) describes the extent to which a patient

appropriately follows medical advice. Mostly, it refers to medication or drug compliance, but it can also apply to medical device use, self care, self-

directed exercises, or other therapy sessions. Both patient and health-care provider affect compliance, and their positive relationship is a major factor in improving compliance.¹ The cost of prescription medication also plays a vital role.² Compliance rates may be overestimated in the medical literature, it is often high in the clinical trial but falls in a "real-world" setting.²

Compliance can be confused with concordance, which is the process by which a patient and clinician make decisions together about treatment. Non-compliance is the biggest hindrance to the effective delivery of health care worldwide. As per the World Health Organization, approximately 50% patients with chronic diseases from developed countries follow treatment recommendations with remarkably lower adherence rates for asthma, diabetes, and hypertension therapies.³ Major obstacles to treatment compliance might include the complexity of modern medication regimens, poor "health knowledge" and misunderstanding benefits, occurrence of side effects, poor satisfaction, cost, and lack of communication and trust between a patient and health-care provider.⁴ Measures to improve compliance may comprise simplifying medication packaging, providing reminders, educating patient, and restricting the number of medications prescribed concurrently. Studies show considerable difference in characteristics and effects of interventions in improving treatment adherence.⁵ It is still uncertain how adherence can be improved to promote clinically important effects.⁶

Materials and Methods

A prospective, observational study was conducted in five general medicine outpatient clinics from 2017 to 2018 in Hyderabad, India. The patients aged 18 years or above presenting to the primary care practice with uncomplicated, suspected acute (<7 days) bacterial pharyngitis and lower respiratory tract infections were enrolled.

Exclusions

The patients who had received previous treatment with antibiotics, who fulfilled criteria for hospitalization, those with condition requiring the aid of other persons for drug administration or, who had hypersensitivity to antibiotics were excluded.

Different antibiotic regimens were packed beforehand in the medication event monitoring system (MEMS) containers and the antibiotic treatments were administered to the patients based on the physician's decision. Before the initiation of the study, the health authorities were informed about its characteristics and process to be followed. The legislation determined that institutional review board approval was not required as it was an observational study.

However, an informed consent was taken from the patients to participate in the study. The patients were provided with complete information regarding the characteristics of the study but, they were not informed about the future assessment of adherence to avoid biasness in the results. During the patient's follow-up visit, the physician collected the MEMS container and self-reported adherence was evaluated by means of the following question: "we almost always forget to take all of the pills, did you ever forget to take any?" and their responses were recorded. Then, the patients were fully informed about the results and their permission was requested to include these data anonymously in the current report¹⁰.

Statistical analysis

All the data included in the database were encoded to ensure confidentiality. The data contained in the microprocessors were transferred to the computer and processed with Power View program v. 1.3.2. (Aardex Ltd.). Multiple openings of the container within a period of less than 15 mins were not counted.

Descriptive statistics were used to describe the different adherence parameters observed in this study. We used Chi-square tests to compare proportions. The sensitivity, specificity, and positive and negative predictive values of the self-

reported adherence question were determined with a two-way contingency table, using the adherence parameters provided by MEMS as the gold standard. A logistic regression model was constructed to identify variables significantly and independently associated with excellent adherence. The variables were included in the model if they were associated with a high score with a p-value of < 0.05.

Results

A total of 60 patients were enrolled. The self-reported adherence question was not registered for 6 patients. Furthermore, 5 antibiotic treatment failures were observed requiring a change in antimicrobial treatment, and the adherence question was not evaluated in these cases. Three

patients did not return the MEMS container and two of these refused to give consent. Hence 44 patients with complete information were for selected for the analysis, of these 26 patients (59.09%) had lower respiratory tract infection and 18 patients (40.91%) had suspected acute bacterial pharyngitis. The mean age of all the patients was of 47.1±21.2 years, which included 24 females (54%).

Of 60 patients enrolled, 24(54.54%) received antibiotics thrice-daily, 15 (34.09%) patients received twice-daily antibiotic regimens, and the remaining 5(11.36%) patients received once-daily antibiotic schedules. The treatment adherence rates with different antibiotic schedules over time are provided below in the Table 1.

Table 1: Treatment adherence rates with different antibiotic schedules over time

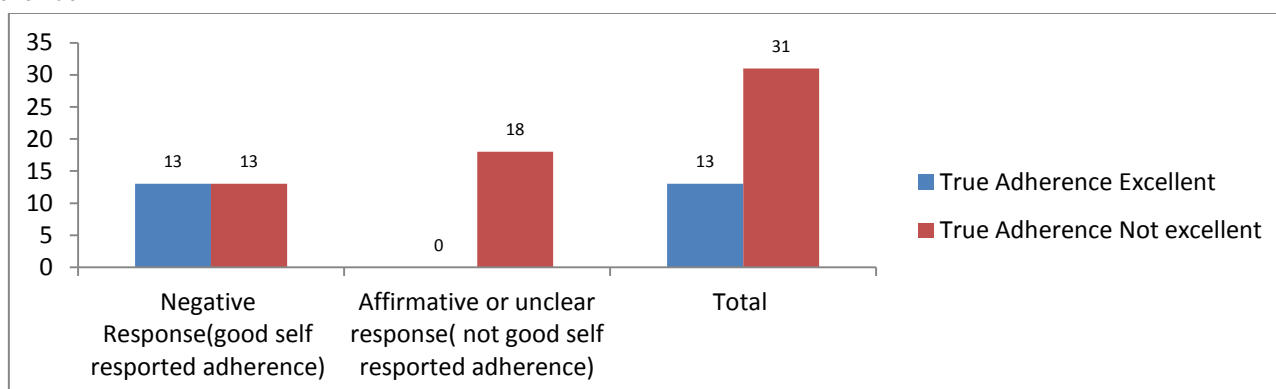
Adherence rates	Once daily antibiotic regimen	Twice daily antibiotic regimen	Thricedaily antibiotic regimen	Total
Excellent adherence	4	8	2	14
Acceptable adherence over time	1	2	3	6
Declining adherence over time	0	3	9	12
Non adherence to consistent correct dosing	0	2	9	11
Unacceptable adherence	0	0	1	1
Total	5	15	24	44

A total of 27 patients opened the vial at least 80% of the times (61.9%), 15 presented correct dosing adherence (34.1%), and 17 achieved good timing adherence for at least 80% of the antibiotic course (38.6%).

A total of 26 patients answered the self-reported adherence question (good self-reported adherence) negatively (59.3%), which is presented in the Figure 1 below. The remaining patients answered

either affirmatively or elicited an unclear response. A total of 31 patients were correctly identified by this approach (70.45%). All patients presenting excellent adherence by means of the MEMS determination reported that they never forget to take their medications. On the other hand, 40.91% patients did not present with excellent adherence.

Figure 1: Response to Self-Reported Adherence Question Classified as Excellent and Not Excellent adherence



Five patterns of antibiotic taking behavior were observed in this study which is presented in Table 2 below: 13 patients (30.4%) achieved 80% of all the adherence outcomes and therefore presented excellent adherence. Another 5 patients (12.4%) missed only one dose for achieving excellent adherence and presented a relatively acceptable adherence during the antibiotic course.

A total of 13 patients (28.7%) presented declining adherence over time with good correct dosing at

the beginning of the antibiotic course followed by a reduction in the daily doses along the remainder of the course until the end. Five of these patients (10.6%) abruptly stopped taking the tablets in the first half of the medication course. A total of 13 patients (28.7%) presented non-adherence to consistent correct dosing over time and 6 (13.3%) presented an unacceptable adherence pattern, with incorrect dosing and a further decline.

Table 2: Antibiotic Taking Behavior and Response to Self-Reported Adherence Question

Antibiotic taking behavior	Response to the self-reported adherence question		Total
	Negative	Unclear response	
Excellent adherence	13	0	13
Acceptable adherence over time	5	0	5
Declining adherence over time	5	8	13
Non adherence to consistent correct dosing	3	10	13
Unacceptable adherence	4	2	6

Candidate variables included in the multivariate regression analysis were the patient characteristics (age, gender, presence of high blood pressure, dyslipidemia, or diabetes mellitus, smoking status, and retired or not) and antibiotic-related variables (daily doses, duration, and presence of adverse effects). Excellent adherence was significantly associated with the number of daily doses of the antibiotic (odds ratio (OR) 0.22, 95% confidence interval (CI) 0.15–0.32) and antibiotic duration (OR 0.77, 95% CI 0.61–0.96).

Discussion

The study compared self-reporting with objectively measured medication adherence using an evidence-based cut-off point in the same study population. The main result of this study is that medication adherence objectively measured by MEMS was very poor since only 30% of the patients presented excellent adherence. Furthermore, the use of self-reported adherence remarkably overestimated the true adherence. Five adherence types were identified in this study by means of the MEMS method: excellent adherence, relatively consistent adherence over time defined as those patients who missed only one dose for achieving excellent adherence, declining

adherence over time, non-adherence to correct dosing, and unacceptable adherence.

In our investigation, poor adherence was associated with patients being discharged with more than one antibiotic, not seeing the same health care provider for care, and not feeling that they had a regular health care provider. These data are consistent with previously reported theoretical constructs and empirical data (Hansen et al)⁷. Other studies found that poor adherence was associated with a higher number of daily doses of the antibiotic (Lloret al)⁸, longer antibiotic treatment duration (Francis et al, Fernandes et al, Llor et al)^{8,9,10}, increasing age, difficulty in buying the antibiotic, duration of treatment, difficulty with ingestion, and satisfaction with the information given by the physician (Fernandes et al)¹⁰.

Notably, we found in our population that the subjects who were more likely to abuse antibiotics without consulting a physician and, in contrast, those who were more prone not to follow the drug protocol as prescribed, had opposing characteristics. In fact, individuals with a lower educational level and occupational status tended to misuse antibiotics while those with a higher level tended to abuse drugs. Other studies

revealed similar (Skiros et al)¹¹ or lower rates (Carrasco-Garrido)¹², but equal predictive factors of self-medicated drug use. Antibiotics are widely used both in the community and in the hospital setting. Nevertheless, their effectiveness is strongly related to how such medications are used by the patients, particularly in the community setting. Previous studies stated that patients reported to discontinue antibiotic therapy when felt better or due to the onset of adverse events (Pechere et al)¹³. The use of recycled medications and the phenomenon of self-prescribing antibiotics are the severe consequences of poor compliance with antibiotic therapy. In our study, we found higher rates for self-prescription than in poor adherence with prescribed antibiotics. Although leftover antibiotics result from a discontinuation of prior treatment, it may also be influenced by the packaging and medication dispensing of the drug. In fact, in countries such as Italy, where drugs require pre-packaged doses of medication, a greater quantity of medication is dispensed than is required, resulting in the availability of leftover doses even after completion of the prescribed regimen (Wright et al)¹⁴. Antibiotic resistance is mainly attributed to the indiscriminate overuse of antibiotics yet doctors may also play a role in this issue. Several investigators have reported inappropriate prescribing practices by physicians in the outpatient setting. Indeed, most of the studies revealed that about half of patients with a common cold are often treated with antibiotics (Gonzales et al)¹⁵, instead of a more discriminate use (Stolz et al)¹⁶. The reasons why physicians inappropriately prescribe antibiotics for conditions that can be cured without using such a therapy can be explained by patient expectations (Macfarlane J)¹⁷.

Hawkings et al.¹⁸ conducted a qualitative semi-structured interview study of 46 people, and reported six different types of antibiotic user behavior: those who always took antibiotics as prescribed, could not take doses because of work, child care, or social constraints, frequently forgot

doses, believed it made sense to stop taking antibiotics as they started to get better, actively sought to limit antibiotic use because they believed their own bodies became used to them or because antibiotics are unnatural, and deliberately planned to stop early so as to have an antibiotic supply for self-use in the future to avoid the challenges of consulting and obtaining antibiotics in primary care. In this study, over one third of the respondents reported that they always took antibiotics as directed by the clinician or pharmacist. The results of the present study clearly indicate that less than a third of the patients took the tablets as recommended. We used the same cut-off point suggested by the previous authors, (Haynes et al)¹⁹ i.e., at least 80% of all the adherence parameters evaluated.

In our study, more than half of the patients with non-adherence to consistently correct dosing and declining adherence over time admitted to have forgotten some doses. Incorrect dosing is more linked to unintentional non-adherence, since it is influenced by the constraints of work, child care, school, and simply forgetting, while declining adherence over time is more associated with intentional non-adherence, and it is more likely that these patients are not aware of the consequences of stopping early.

Despite being unintentional, patients who systematically forgot to take a pill every day were more aware of being non-adherent than those who had a priori intentional non-adherence, since nearly 80% of the former respondents admitted having forgotten to take some doses versus. 60% of the latter who did so. Patients who stopped taking antibiotics as they started to get better, those who limited their use because of some misbeliefs, and those who planned to have an antibiotic supply at home are supposed to have excellent adherence at the beginning of treatment and a deteriorating adherence after some days, but curiously only 10% of these patients stopped the treatment very soon. The remaining 90% of these patients actually decreased the frequency of the doses after a period of perfect adherence. This

probably means that most of the patients with declining adherence over time were aware that taking the antibiotics was necessary and felt guilty about stopping to take them. The number of adherence types is likely to vary with the study population under analysis. In studies involving long-term conditions, other typologies of medication use behavior have been detected, such as improving adherence over time. For example, Knafelz et al.²⁰ identified 10 adherence types for subjects with HIV on antiretroviral medications, including seven relatively consistent, one deteriorating, and two improving adherence types. However, with treatment lengths up to 10 days, such as the schedule addressed in our study, the number of medication use behaviors is much lower, with three typologies being the most common – one of good adherence and two basic patterns of non-adherence. We only included outpatients with relatively benign acute conditions and this fact might explain why so many patients failed to present excellent adherence behavior. Another conclusion of this study is that medication adherence measured by the self-reported adherence question was remarkably higher than that objectively measured by MEMS, indicating that self-reporting seems to be prone to overestimating of true adherence.

To our knowledge this is the first time that a self-reported question has been used to report the adherence of patients in acute infectious diseases. The main explanation that may underlie the difference between self-reported and 'true' adherence is that patients may not want to admit that they are non-adherent, and therefore reported adherence. Self-reported adherence is able to detect non-adherence when the patient reports forgetting some doses, since a patient who admits not having forgotten any dose can be either adherent or non-adherent with respect to timing and dosing. Therefore, this screening question has little value in clinical practice. The diagnosis was clinical and therefore it cannot be guaranteed that all the episodes included were actually bacterial infections; however, this could have happened

equally in all the treatment regimens and should not be directly related to the adherence to treatment. Nonetheless, we believe that the electronic method used in this study, the large sample studied, and the fact that the patients were not informed as to the real objective of the study until the second visit, undoubtedly constitute the greatest strengths of this study.

Conclusion

Less than half of the patients treated with regular courses of antibiotics presented excellent or acceptable adherence. Approximately one in four patients presented non-adherence to correct dosing and approximately one in four presented declining adherence over time. The adherence outcomes were consistently and significantly worse with three times-daily antibiotic schedules and better with once-daily antibiotic regimens. The self-reported adherence question presented a significant negative predictive value but its low positive predictive value makes this method inappropriate for use in clinical practice.

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