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A study of medication adherence in apparent treatment-resistant hypertension in India

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Abstract

Background: Despite increased awareness, poor adherence to treatments for chronic diseases remains a global problem. Adherence issues are common in patients taking antihypertensive therapy and are associated with Increased risks of coronary and cerebrovascular events. **Aim and Objective:** The present study aimed to analyze medication adherence and its effect on blood pressure (BP) control and assess the prevalence of treatment-resistant hypertension (TRH) among newly treated hypertensive patients. **Method and Material:** A cross-sectional, observational study was conducted in department of general medicine, Rani Durgawati Medical College, Banda, Uttar Pradesh. 100 adults (age 18 years) with hypertension on treatment for at least 6 months, fulfilling the criteria of apparent treatment resistance, were **Observation and Result:** Males constituted 70% and females constituted 30% of the study population. The mean age was 52.11 years. 48% were diabetics, 38% had CKD, 27% had COPD, and 22 had CKD. 51% were smoker, and 18% were alcoholics. Almost all the patients with aTRH were found to have low adherence (98%). Female s ex, financial dependency, lower socioeconomic status, alcohol, smoking, knowledge about medication and the presence of depression were significant factors associated with low medication adherence in a RTH. **Conclusion:** Our study find that significant low medication adherence among patients with TRH. The study stresses that medication adherence be checked in each and very aTRH patient, and specific underlying causes must be addressed

Key words: M*edication* A*dherence*, Hypertension, Blood Pressure

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Introduction

Apparent Treatment-Resistant Hypertension (aTRH) is defined by a BP > 140/90 despite the use of three classes of anti hypertensive medications or the use of four or more anti hypertensives regardless of blood pressure. Pseudo resistance is the most common form of resistance in clinical practice [1]. It implies the absence of true resistance to drugs and is due to either measurement errors, poor adherence to treatment or the white-coat effect, or fragmented health services.

Worldwide, 874 million adults suffer from an office SBP of 140 mmHg or higher, which is associated with an annual death rate of 106 per 100,000 patients [2]. For the pharmacological control of hypertension, adherence to blood pressure (BP)-lowering drugs is essential. Poor adherence is associated with a higher residual cardiovascular risk (for the patient) and a high healthcare burden due to the greater effort to improve BP with additional diagnostic tests and interventions, such as renal denervation (RDN) [3–4]. However, Indian data on this aspect is sparse. It is generally believed that aTRH patients are at greater risk for poor outcomes compared to the general hypertension population [5]. Many individuals with ATRH may not undergo a comprehensive assessment of the causes. Low patient adherence to antihypertensive medication is the most significant modifiable patient-related barrier to achieving controlled blood pressure [6].

Previous cross-sectional studies published information on factors of on adherence in patients with hypertension [7]. However, almost all studies on adherence in hypertension are based on the self-assessment Morrisky questionnaire, a method shown to overestimate adherence and to be potentially biased. In contrast, the results of objective adherence measurements using drug screening in urine and blood are unbiased. In general, the assessment based on screening in urine provides information on long-term use, while detection in serum can be considered indicative of short-term drug intake [8]. From a pharmacological perspective, the latter is more related to BP measurements performed within the same time frame as sample collection [9]. Many studies have reported low adherence to antihypertensive medication to be associated with worse BP control [10–12]. Identifying the associated factors can help target future interventions to improve adherence in people with aTRH. The exact prevalence of resistant hypertension is unknown in India. In a study by Mandal et al., 23.33% (300 sample size) were identified as having apparent treatment-resistant hypertension [9]. Older age groups (>55 years), obesity (BMI > 27.5 kg/m2), diabetes mellitus, prolonged hypertension (>10 years), and co-morbidities like ischemic heart disease are some of the risk factors associated with resistant hypertension. In the Framingham study, in the Indian data, the strongest predictor of lack of control was older age, with participants >75 years being less than one fourth as likely to have systolic BP controlled compared with participants 60 years of age. For both systolic and diastolic BP, the next strongest predictor was obesity, with one-third less control than lean participants [13].

Genetic assessments of patients with resistant hypertension are limited. A particular CYP3A5 allele (CYP3A5*1) has been associated with African American patients with higher systolic pressures and treatment resistance [1]. The prognosis for resistant hypertension compared to controlled hypertension has not been specifically evaluated. Presumably, the prognosis is impaired in the former due to a long standing history of

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poor control and associated risk factors such as diabetes, obstructive sleep apnea, left ventricular hypertrophy (LVH), and/or CKD. The degree to which cardiovascular risk is reduced with the treatment of resistant hypertension is unknown. The benefits of successful treatment, however, are likely substantial, as suggested by hypertension outcome studies such as the Veterans Administration cooperative studies [14].

Medication adherence is defined as "the extent to which the medication-taking behavior of a patient corresponds with agreed-upon recommendations from a DIEa health care provider" [15]. It is an important factor in achieving blood pressure control [16]. Unfortunately, poor adherence to medications is widespread, especially in the treatment of chronic conditions such as hypertension, leading to poor health outcomes and huge medical spending on drug-related morbidity [17]. As reported by the World Health Organization, adherence to medication in patients with chronic diseases averages only around 50% in developing countries. The situation is reported to be worse in developing countries due to poor accessibility to medications and health care services [16]. The asymptomatic nature of the condition intensifies the problem of non-adherence in hypertension [18]. Factors that affect adherence are demographics, the severity of the disease, the complexity of the drug regime (number of drugs and daily doses prescribed), drug classes (tolerability and side effects), patients' forgetfulness, and a lack of understanding [19]. However, the results reported in previous studies have not been consistent. Adherence to treatment can be measured using different methods, like pill counting, drug concentration in the body fluids, and response to therapy, involving electronic medication packaging (EMP) devices and measures involving clinician assessments and self-report. There is no single measure for medication adherence that is user-friendly, easy to execute, reliable, flexible, and practical at once. One of the easier and best-validated tools is the Morisky Medication Adherence Scale (MMAS-8). It is probably the most accepted self-report measure available, along with blood pressure control data, and therefore was used in the study.

Materials and Methods

The present study was conducted in the OPD and special clinics in the Department of Medicine, Rani Durgawati Medical College, Banda, Uttar Pradesh, from September 2023 to February 2024. It was a prospective cross-sectional study. Adult subjects (age ≥18 years) who were hypertensive and on treatment for at least six months, fulfilling the criteria of apparent treatment-resistant hypertension, were included in the study after informed consent. All pregnant women and patients with a recent change in medications or dosage (less than a month) were excluded. The study was approved by the Institutional Ethical Committee.

Methodology:

Apparent treatment-resistant hypertension is defined as blood pressure ≥ 140/90 mmHg on 3 or more anti-hypertensives or controlled blood pressure on 4 or more anti-hypertensive medications, at optimal doses and preferably including a diuretic. A case record form was filled out for each subject. Weight was measured in kg using the weighing scale. Waist circumference was measured in centimeters at the level of the highest point of the iliac crest. and central obesity was defined as waist

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circumference >90cm for South Asian men and >80cm for South Asian women. Height was measured with a fixed stadiometer.

BMI was calculated as weight divided by height squared (kg/m2). Two consecutive resting seated blood pressures (BP) were recorded 10 minutes apart using automated BP instruments. The previous values were taken from their medical records, if available. Relevant demographics details along with detailed treatment histories were collected, including drug names, their respective doses, and any side effects.

For medication knowledge, subjects were asked five questions about each medicine being taken, including the name, dose, frequency, indication, and how and when the drug was taken. The knowledge score ranged from 0 to 5 by summing the responses to the five questions (1=yes, 0=no) [20]. Patients were interviewed for medication adherence as per the Morisky Medication Adherence Scale (MMAS-8). Patients were made to answer eight questions related to adherence behaviors, with a composite score of 8/8 indicating high adherence, 6 to <8/8 moderate adherence, and <6/8 low adherence. The presence of depression was assessed as per the PHQ-9 scale [21].

Outcome Measures

The study's primary outcomes include adherence to anti hypertensive treatment, changes in the BP from baseline to six months, and BP control at 6-month follow-up. In the secondary analysis, we determined the prevalence of TRH in patients adherent to medications and PRH in patients non adherent to anti hypertensive treatment.

Data Collection

Data collected at the baseline line included age, sex, healthcare center location (rural or urban), type of health facility (primary, secondary, and tertiary), smoking status (smoker or non-smoker), body mass index (BMI, kg/m2), and diabetes mellitus (DM) status. Along with the BP parameters, the data collected at baseline and six months included the number and type of anti hypertensive drugs prescribed and pharmacy refilling information.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics software for Windows, version 16.0 (IBM Corp., Armonk, NY, USA). The baseline characteristics were presented as frequency and percentages for categorical variables. The mean ± standard deviation (SD) was used for continuous variables. The chi-square test was used to compare the differences between categorical variables, and the ANOVA or Kruskal-Wallis test was used for continuous variables, as appropriate. A Wilcoxon-signed rank-sum test was used to determine if there was a significant difference between baseline and six months across various categories.

Observations and Results

For the present study, 100 patients met the inclusion criteria. The mean age was 52.11 years (SD = 11.07). Of the total subjects, 30% were females and 70% were males. 81% of cases were married, and 19% were unmarried. 56% were members of nuclear

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families, with the remaining 44% belonging to joint families. 73% of cases were financially dependent on other family members, while 27% were financially independent. Prasad's social classification (*revised for 2017) was used for the socioeconomic status classification of the study participants [21]. 52% belonged to the upper-middle class (class II). Among comorbidities, diabetes mellitus was the most common comorbidity, followed by CKD and COPD (table no. 2). Among 100 patients, 18% were alcoholics, and 51% were smokers.

Table no. 1: Knowledge about medicine in the study population:

Aspects of knowledge about medicine	Number (percentage) of participants
Name of medicine	11 (11%)
A dose of the medicine	23(23%)
Frequency of dosing	55 (55%)
Indication of drugs	73 (73%)
How and when to take	67 (67%)

Table No. 2: Co-morbidity in Patients

Co-morbidity	**Number (percentage) of participants**
Diabetes mellitus	45%
CKD	29%
Chronic obstructive airway disease	25%
CAD	19%
Cerebrovascular accidents	13%

Table No. 3: Prescribed Anti hypertensive

Prescribed Anti hypertensive,	**%**
Calcium channel blocker	**0.95**
beta-blockers	**0.6**
Diuretics	**0.55**
ACE inhibitors	**0.46**

Calcium channel blockers were the most commonly prescribed antihypertensives, followed by beta-blockers, diuretics, and ACE inhibitors **(table . 3)**. Knowledge regarding the indications of the drug, followed by how and when to take the drug, were the least recollected aspects **(Table** no. 1**)**.

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Table no. 4: Response to 8 questions about MMAS in the study population

Morisky medication adherence scale	Yes	No
	N	N
Do you sometimes forget to take your hypertension medication?	33	67
Over the past two weeks, were there any days when you did not take hypertension medication?	35	65
Have you ever stopped taking your medications or decreased the dose without first warning your doctor because you felt worse when you took them?	53	47
When you travel or stay at home, do you sometimes forget to take your medications?	40	60
Did you take your blood pressure medication yesterday?	18	82
When you feel your blood pressure is controlled, do you sometimes stop taking medication?	26	74
Have you ever felt distressed about strictly following your high blood pressure treatment?	16	84
How often do you have difficulty remembering to take all your blood pressure medications?	Graded response	Graded response

Medication adherence was assessed through a self-administered questionnaire using the MMAS-8 adherence scale, which consisted of 8 questions. The response score is shown in Table 4.

Tableno.5: Association of age, gender, alcohol consumption, smoking, and knowledge about medication score with medication adherence in the study population:

Different Parameters		N	Mean MMAS Score	SD	P-Value
Age-Group	Age: <60 years	75	2.9	0.58	0.000
	Age >60 years	25	3.55	0.48	
Gender	Females	30	2.53	0.46	0.001
	Males	70	3.04	0.81	

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Alcohol consumption	Absent	82	3.25	0.9	5.79
	Present	18	2.05	0.65	
Smoking	Non smokers	49	3.69	0.61	0.000
	Smokers	51	2.48	0.44	
Knowledge about medication scores	<3	52	2.82	0.71	0.042
	3 to 5	48	3.13	0.8	

After this, the MMAS total score was calculated. The observed score ranged from 0 to 8, categorized into low, medium, and high adherence groups. It was found that almost all, except two patients, had low adherence (98%). The two had medium adherence, and none had high adherence. It was found that MMAS was more prevalent in patients >60 years compared to those <60- years -old, but this was not statistically significant **(Table** 5**)**. The mean MMAS score for adherence was better in males compared to females, and the result was statistically significant **(Table** 5**)**. The association of BMI, or waist circumference, marital status, and education status with medication adherence was found to be statistically insignificant. Patients who were financially independent had a lower mean adherence score compared to those who were financially dependent, and the result was statistically significant. Socioeconomic status as classified according to the modified BG Prasad classification [22, 23] was dichotomized as upper class (includes upper and upper-middle-class) and lower class (includes lower middle and middle class). The mean adherence score was better among those patients belonging to the upper class compared to those belonging to the lower class, and the result was statistically not significant. The mean adherence score was much better among those with alcohol consumption (p-value = 5.79) **(Table** 5**)**. The mean adherence score was low among smokers compared to non-smokers, and the result was statistically significant with a p-value of 0.000 **(Table** 5**)**. Patients were categorized according to those having a knowledge score less than 3 and those having a score of 3 or more. Patients with a lower knowledge score also had a lower mean MMAS score compared to those with a higher knowledge score, where the mean adherence score was also higher (p = 0.042). Mean adherence was compared with individual items of knowledge score to see the association (**Table** 5**).**

Table no. 6: Association between individual questions on knowledge about medic ation and mean adherence score:

The stem of each question about knowledge	**Mean adherence score among those who knew and among those who did not know**		
	Who knew	**Who did not know?**	**P – value**
Name of medication	3.8	2.85	0.020
Dose of medication	3.6	2.81	0.67
Frequency of medication	3.2	2.65	0.78
Indication of medication	3.3	2.5	0.44
How and when should I take the medication?	3.15	2.45	0.007

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Among five questions about knowledge about medicine, how and when to take the medication was associated with the statistically significant MMAS adherence score **(Table** 6**)**.

TableNo7: Association of depression, diabetes, and CAD with medication adherence in the study population:

			Mean MMAS Score	SD	P-Value
Depression	Absent	(33%)	3.54	0.46	0.00004
	Present	(67%)	2.83	0.9	
Diabetes Mellitus	Absent	(52%)	2.98	0.92	0.036
	Present	(48%)	3.14	0.82	
Coronary artery disease	Absent	(62%)	3.22	0.74	0.017
	Present	(38%)	2.83	0.85	

For analysis, we categorized patients with depression (67%) and patients without depression (33%). The medication adherence score was compared with the presence and absence of depression. The mean adherence score was better among those who did not have depression (p = 0.00004) **(Table** 7**)**. The mean adherence was better among diabetics (48%) compared to non-diabetics (52%), and the result was statistically significant (p = 0.036). Patients who had known h/o coronary artery disease had a better mean MMAS adherence score compared to those who did not (62%); the association was statistically insignificant. (p=0.017).

Discussion

This study was conducted among patients with apparent treatment for resistant hypertension. A sample size of 100 patients was recruited. The main objective of the study was to determine the prevalence of medication adherence among patients with ATRH. Medication adherence was assessed using the MMAS-8 questionnaire method. Also, various factors associated with medication adherence were studied and looked at for a correlation. Several important results about medication adherence in patients with aTRH were found in our study. In our study, the prevalence of low adherence was found to be 98% (n = 100); almost all the study population had low adherence to their medication. Although no Indian studies are available about the prevalence of medication adherence among aTRH, foreign studies showed a prevalence in the range of 9.9 to 68% [20–24]. In the latest meta-analytic study conducted by Durand et al. in 2017, the prevalence of non-adherence varied between the studies, ranging from 3.3% to 86.1% [25]. The reasons for very low adherence in our sample may be due to poor education, lower socioeconomic class, and poor knowledge about the disease and medicine.

Age is an independent risk factor for hypertension as well as resistant hypertension, which is associated with high mortality and morbidity. The mean age of the population in our study was 52.11 ± 11.07 years. In a study by Stacie et al., the mean age was 60 years (25th quartile =51, 75th quartile = 70) [26]. In a study by Garg et al.,

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the average age was 57±13 [27]. In our study, the mean age was lower compared to other studies. In this study, 70% of recruited patients with aTRH were males, and 30% were females. In a study conducted by Irvin et al., among 2654 patients with aTRH, 48.2% were males [28]. The most common comorbidity was diabetes mellitus (48%), followed by chronic kidney disease (CKD) (38%). Irvin et al. found 49.6% of diabetics and 48% of CAD patients in their study.

The secondary objective was to determine the association between various socio-demographic and clinical factors and medication adherence. The mean adherence score was found to be good in patients aged more than 60 years, compared to less than 60-year-old patients. Non-adherence in younger patients may be due to the lack of persistent symptoms at the early stages of the illness or to concerns about medication side effects. In a study conducted by Patel and Taylor in 2002 [29], among 240 patients with hypertension, there was no statistically significant difference in medication adherence based on age, gender, education, total household income, living arrangements, or the total number of years with hypertension or medications. Since studies to compare factors affecting medication adherence in aTRH were nil, we have tried to compare results with medication adherence among hypertension. In a study conducted by Karakurt et al. in 2012 [30], the prevalence of non-adherence was 57.9%, with a significant association between old age and non-adherence.

In the present study, the mean MMAS score was higher in males than females, implying better adherence. In a study by Gupta et al. [31] in the UK in 2016, females were found to be more non-adherent compared to males. These results were, in contrast, to those of the study conducted by Ramli et al. [32]. In 2012, in Malaysia, using MMAS-4 as a measure, female patients were found to be one and a half times more likely to be adherent than male patients (odds ratio 1.38 [95% CI: 1.00–1.90; P-0.05]). Thus, studies have shown variable results with regards to sex as a risk factor. Unmarried patients with aTRH had a better adherence score compared to married patients. This is in contrast to the study by Venkatachalam et al. [33], where the married respondents were more adherent compared to the unmarried. Among patients with aTRH, financially dependent patients had a better mean adherence score compared to financially independent patients, the reason for which might be that most of the financially dependent patients belonged to the older age group, which showed higher adherence. Most patients with aTRH belonged to the upper-middle (52%), and middle-class (48%). In this study, the mean adherence score was lower in a lower socioeconomic class compared to the upper class. In a systematic review and meta-analysis study by Alsabbhag et al. [34], higher socio-economic status (SES) was associated with a lower risk of non-adherence in 31 out of 40 cohorts (77.5%). The importance of the SES as potential risk indicators of non-adherence may also be under-recognized. Our understanding of the complex relationship between SES and medication adherence is likely incomplete because it is based on studies using a limited set of SES measures, at least in studies focused on antihypertensive medication.

Alcoholics had a lower adherence score compared to non-alcoholics ($p = 0.000$). Many studies did not look for the association of medication adherence with alcohol intake in patients with aTRH or hypertension per se. However, alcoholics appear to have poor adherence due to poor concern for their health status and poor compliance with advice and follow-up. Similarly, smokers too had a lower adherence score

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compared to non-smokers. This was similar to Venkatachalam et al. [35]. The respondents exhibited poor adherence to lifestyle factors like unrestricted meal habits (OR = 4.8), alcohol consumption (OR = 3.1), and smoking (OR = 12.9). Smoking remains a key modifiable risk factor for both better control of hypertension and improving medication adherence.

Knowledge about medicine is a very important factor in determining medication adherence. Patients with a low knowledge score had a lower adherence score. Individual questions about medication, such as how and when to take medicine, were strongly associated with medication adherence. Ramli et al. [34] in 2012 showed that there was an established relationship between medication knowledge and drug adherence (odds ratio = 1.03; 95% CI = 1.01–1.04; p = 0.01). They also showed that the odds of adhering to medication were modestly improved with a point increase in the knowledge score for the medicines. Getting patients involved in the treatment by educating them greatly improves adherence.

It was also seen that the presence of any level of depression was associated with a lower mean adherence score. A similar result was found in a study by Siegel et al. [35]. They found that patients with an ICD-9 diagnosis of depression in their medical record were less likely to be adherent (odds ratio [OR] =0.86, p<0.01). The mean MMAS score was higher among diabetics compared to non-diabetics, whereas Ramli et al. [34] found diabetics to have poor adherence. Patients with CAD had a lower mean adherence score. Implying marked variability in comorbidity associations. Further studies are needed to ascertain whether complex treatment regimens and/or persistence of behaviors are associated with low adherence.

In our opinion, the study had a few limitations. The adherence scale was not specific to anti hypertensive medications, and adherence was assessed only at a single point in time. Additionally, the assessment was based on self-report and therefore subject to bias. Electronic data on medication adherence (e.g., pharmacy fill data) was not available in our study. While the eight items in MMAS were validated, participants may have provided socially desirable responses. Pill burden might have been another factor to be considered.

Conclusion:

Almost all the patients with aTRH were found to have low adherence (98%). As a factor associated with medication adherence in aTRH, there was a significant association between low medication adherence and female sex, financial dependency, lower socioeconomic status, alcohol use, smoking, a lack of knowledge about medication, and the presence of depression.

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