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Possible Effects of Medication Regimen on Non-Adherence to Antihypertensive Therapy

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Abstract

Purpose: Poor control of Blood Pressure (BP) may be attributable to many factors; non-adherence is considered a main cause for inadequate BP control. The study aimed to investigate the potential effects of medication regimen on adherence to antihypertensive therapy and explored BP profiles of hypertensive patients disaggregated by the level of medication adherence.

Methods: A retrospective cohort study of electronic medical records of hypertension outpatients in Taiwan. We surveyed 604 adult (age ≥ 30 years) outpatients with hypertension using structured questionnaires and measured BP and physiological parameters. Chi-square test and Fisher's exact test for categorical variables and analysis of variance for continuous variables were performed to assess differences among patients with high, medium and low level of medication adherence. Multiple regression analysis was used to examine the relationship between BP and adherence after controlling for potential confounding factors.

Results: Significant difference was found among the three groups with respect to the number of sources of medications, dosage forms, duration of hypertension, age, education, marital status, employment, Systolic BP (SBP), Diastolic BP (DBP) and Mean Arterial Pressure (MAP) ($P<0.05$ for all). Multiple sources of medications had a significant adverse effect on adherence ($\beta= -1.06$, $P<0.01$). Adherence was a predictor of SBP ($\beta= -0.60$, $P=0.03$), DBP ($\beta= -0.32$, $P=0.04$) and MAP ($\beta= -0.41$, $P=0.02$).

Conclusion: Multiple sources of medication were associated with poor adherence to antihypertensive therapy, which was found to predict the level of BP control.

Keywords: Hypertension; Blood pressure; Antihypertensive therapy; Adherence; Regimen

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Introduction

Hypertension significantly increases the risk of complications, including cardiovascular diseases, stroke, diabetes, renal failure and retinopathy [1-4]. Globally, an estimated one billion people are affected by hypertension; and it accounts for approximately 7.1 million deaths annually [5-7]. Hypertension is among the ten top leading causes of death in Taiwan; in 2014, hypertension accounted for 5459 deaths (23.3% of total deaths) in Taiwan [8]. Therefore, hypertension is a major public health issue in Taiwan.

Taiwan's National Health Insurance (NHI) is a mandatory nationwide health insurance program implemented in 1995 [9-11]. According to the NHI data, antihypertensive medications accounted for US $0.61 billion out of the total US $4.5 billion reimbursements for medication costs in the year 2010. The cost of antihypertensive medications has continued to increase, and the growth rate in the year 2010 was approximately 3.5% [12]. According to the American Heart Association, the total cost of hypertensive treatment in the United States in 2010 was US $46.4 billion, of which antihypertensive medications accounted for at least US $20 billion [13].

Poor control of Blood Pressure (BP) may be attributable to many factors including excess weight, excess salt intake, excess alcohol, smoking, lack of exercise, environmental stress, inadequate

treatment regimens, complications and non-adherence [1,7,14-17]. Among these, non-adherence is considered a main cause for inadequate BP control [1,7,16]. Several factors impair adherence to prescribed therapies, including demographic characteristics, complexity of medication regimen, adverse events, behavioral factors and other clinical variables [18,19]. Non-adherence to antihypertensive therapy is a complex health behavior [20,21]. Although up to half of all hypertensive patients may regularly take their medications, only 50% to 60% of these patients showed optimal BP control [22-25]. In the studies by Bangalore et al. [26] and Morgan et al. [27], adherence to antihypertensive treatment varied from 50% to 60%.

The purpose of this study was to investigate the possible effects of medication regimen on non-adherence to antihypertensive therapy and to explore the BP profile of patients who adhere to antihypertensive therapy.

Methods

Study population

In one year, a total of 604 outpatients [275 male (age range: 32 to 96 years) and 329 female (age range: 31 to 91 years)] were enrolled at a Regional Hospital in Taiwan. The inclusion criteria were: (1) age ≥ 30 years; (2) diagnosis: HTN; (3) patients receiving at least one antihypertensive drug; (4) self-administering medications without prompts from other person; and (5) patients who were able to converse. Patients with any mental disorder, chronic medical condition with a life expectancy of <6 months, or poor understanding of the intent of the study were excluded.

Study participants were estimated to be sufficiently representative of the population living in eastern Taiwan, since the regional hospital where patients from every socioeconomic class in Taiwan's east are admitted. The regional hospital of Clinical Investigation, which is composed of the Institutional Review Board, approved the study. Among 604 eligible participants approached for written informed consent and volunteered to participate.

Study design

This was a cross-sectional study conducted from three months. The study employed a random sampling technique. Data was obtained using a structured interview questionnaire, hospital electronic record system, medical charts of individual patients and measurements of BP and physiological parameters. Each interview lasted for approximately twenty minutes. The questionnaire included information concerning demographic variables, medication regimen, medical history, health-related behavior and measures of medication adherence. The questionnaire was pilot tested in a group of ten hypertensive patients to identify any ambiguous and unclear wording in the questionnaire. Some minor adjustments were made to the questionnaire after the pilot test.

Measurements of Variables

The study variables including medication adherence, medication regimen, potential confounding factors and BP values were analyzed.

Medication adherence

Adherence was measured using self-report and the measure was based on the medication adherence questionnaire. The total scores in the adherence questionnaire ranged from zero to eight, with each item measuring a specific medication-taking behavior and not a determinant of adherence behavior. The sixth survey item required a yes (1) or no (0) response from the patient. Other seven items consisted of a four-point response: never (1) and once in a while/sometimes/all the time (0). The questionnaire has been dichotomized previously into three groups of adherence to facilitate use in clinical settings: high (total score: 8); medium (total score 6 to <8); and low (total score <6). The medication adherence questionnaire was found to have a high reliability in our study population (α=0.83, 95% CI=0.81-0.85, P<0.05). Confirmatory factor analysis using maximum likelihood extraction method with varimax rotation showed that one factor accounted for 39% of the variance. All factors loaded above 0.3 for the eight items. Medication adherence rate was calculated by the formula: Adherence rate (%) = [(number of patients in high adherence group + number of patients in medium adherence group)/number of all participants] × 100.

Medication regimen

Data pertaining to variables related to medication regimen were obtained from each participant's self-report and hospital electronic record system for the previous six months. These included the type of medication, pill count, dosage frequency, dosage forms, and side effects of antihypertensive drugs and sources of medications.

Confounding factors

Demographic variables included age, gender, education status, marital status, residence, financial status and employment status. Medical history included hypertension-related complications, duration of hypertension, use of Complementary and Alternative Medicine (CAM) and Drug-Drug Interactions (DDI). Data pertaining to DDIs were obtained from the hospital electronic record system.

Variables pertaining to health behavior included alcohol intake, smoking, betel nut chewing, regular exercise, sleeping status, diet, stress, body mass index and self-management of BP. Body Mass Index (BMI) was calculated by measurement of height and weight (kg/m^2), and patients were classified into four groups (<18.50: underweight; 18.50 to 24.99: normal range; 25.00 to 29.99: overweight; ≥ 30.00: obese) based on the international classification for adults based on WHO data for 1995 to 2004 [28]. Stress was assessed using the Chinese version of the Patient Health Questionnaire (PHQ-9) [29]. The PHQ-9 consists of 9 items, which evaluate the presence of one of the nine DSM-IV criteria for depressive episode in the past 2 weeks. Each item of the PHQ-9 requires a response on a 4-point scale, ranging from 0 (never) to 3 (nearly every day); the total score ranges from 0 to 27, with higher scores indicating an increased likelihood of depression [29]. The PHQ-9 showed a high reliability in our study population (α=0.86, 95% CI=0.85-0.88, P<0.05). Confirmatory factor analysis using maximum likelihood extraction method with varimax rotation revealed that one factor accounted for 42% of the variance. All factors loaded above 0.4 for the nine items.

BP values

After the participant had completed the questionnaire, one sitting BP measurement was taken in the right arm with an electric sphygmomanometer after an interval of 5 min. Two BP measurements in the last 6 months were obtained for each patient from the chart, and the average of the three readings was used to determine the BP level. The Mean Arterial Pressure (MAP) was obtained from the SBP and DBP levels using the formula: MAP=[(2 × DBP)+SBP] divided by 3 [30]. The average reading of <140/90 mmHg was considered indicative of controlled hypertension [1,7,16].

Table 1: Demographic characteristics of patients disaggregated by level of medication adherence.

Variables	All (n=604)	High (n=166)	Medium (n=181)	Low (n=257)	*P*
Age, mean (SD), y	64.7 (12.4)	66.4 (12.0)	66.0 (12.3)	62.6 (12.5)	<0.01
Gender, n (%)					0.05
Male	275 (45.5)	89 (53.6)	79 (43.6)	107 (41.6)	
Female	329 (54.5)	77 (46.4)	102 (56.4)	150 (58.4)	
Education, n (%)					0.02
Less than elementary school	79 (13.1)	26 (15.7)	17 (9.4)	36 (14.0)	
Elementary school	241 (39.9)	54 (32.5)	56 (21.8)	100 (38.9)	
Junior high school	81 (13.4)	30 (18.1)	23 (12.7)	28 (10.9)	
Senior high school	123 (20.4)	33 (19.9)	34 (18.8)	56 (21.8)	
University	68 (11.3)	23 (13.9)	16 (8.8)	29 (11.3)	
Graduate degree and above	12 (2.0)	0 (0.0)	4 (2.2)	8 (3.1)	
Marital status, n (%)					0.04
Single	38 (6.3)	8 (4.8)	7 (3.9)	23 (8.9)	
Married	428 (70.9)	117 (70.5)	131 (72.4)	180 (70.0)	
Widowed	104 (17.2)	31 (18.7)	37 (20.4)	36 (14.0)	
Divorced	26 (4.3)	10 (6.0)	5 (2.8)	11 (4.3)	
Separated	6 (1.0)	0 (0.0)	0 (0.0)	6 (2.3)	
Living with someone	2 (0.3)	0 (0.0)	1 (0.6)	1 (0.4)	
Residence, n (%)					0.77
Living alone	67 (11.1)	12 (7.2)	24 (13.3)	31 (12.1)	
Living with families	524 (86.8)	150 (90.4)	153 (84.5)	221 (86.0)	
Living with friends	6 (1.0)	2 (1.2)	2 (1.1)	2 (0.8)	
Living facilities	4 (0.7)	1 (0.6)	1 (0.6)	2 (0.8)	
Others	3 (0.5)	1 (0.6)	1 (0.6)	1 (0.4)	
Financial status, n (%)					0.2
Upper	131 (21.7)	41 (24.7)	41 (22.7)	49 (19.1)	
Middle	336 (55.6)	93 (56.0)	105 (58.0)	138 (53.7)	
Lower	137 (22.7)	32 (19.3)	35 (19.3)	70 (27.2)	
Employment, n (%)					<0.01
Full-time	137 (22.7)	25 (15.1)	36 (19.9)	76 (29.6)	
Part-time	50 (8.3)	11 (6.6)	13 (7.2)	26 (10.1)	
Unemployed	417 (69.0)	130 (78.3)	132 (72.9)	155 (60.3)	
Adherence score, mean (SD)	5.4 (2.4)	8.0 (0.0)	6.6 (0.5)	3.0 (1.6)	<0.01

SD: Standard Deviation

Sample size calculation

Sample size was obtained using F test and multiple regression analysis in G*Power 3.1.9.2. Using an a priori power calculation, a sample size of 400 was required to detect a 50% medication adherence rate with 80% statistical power using two-tailed tests at a significance level of α=0.05. After assuming an attrition rate of 20%, a total of 480 participants were required for the study.

Statistical analyses

Descriptive statistics were calculated for all measures as appropriate. Categorical variables are presented as frequency and percentage, while mean and standard deviation were calculated for continuous variables. The differences between low, medium and high adherence groups with respect to demographic characteristics, medication regimen and other variables were assessed by chi-square test. Fisher's exact test was used to assess between-group differences with respect to categorical variables and t test or analysis of variance used for continuous variables. Bonferroni's post hoc test was used to determine significant differences between the three groups. Multiple regression analysis was performed to examine possible effects of medication regimen on non-adherence. The relationship between BP and adherence was assessed using a Multivariate Linear Regression (MLR) model, in which BP was predicted as a function of adherence after controlling for potential confounding factors. All data analyses were performed using the SPSS 20.0 software (SPSS Inc, Chicago). The significance level was set at P less than 0.05 and all tests were two-tailed.

Results

Mean participant age was 65 (SD=12.4) years (Table 1); 54.5%

Table 2: Medication regimen and medical history of participants disaggregated by level of adherence to antihypertensive therapy.

Variables	All (n=604)	High (n=166)	Medium (n=181)	Low (n=257)	*P*
No. of medications, mean (SD)					
All drugs	4.9 (2.6)	5.2 (2.9)	4.9 (2.6)	4.6 (2.5)	0.1
HTN drugs	1.6 (0.8)	1.7 (0.8)	1.6 (0.7)	1.6 (0.8)	0.13
Pill counts, mean (SD)					
Pills with all drugs	7.8 (5.4)	8.2 (6.1)	8.1 (4.9)	7.3 (5.2)	0.15
Pills with HTN drugs	2.3 (1.4)	2.5 (1.5)	2.2 (1.4)	2.3 (1.3)	0.2
Frequency with HTN drugs (daily), mean (SD)	2.5 (1.9)	2.6 (1.8)	2.4 (1.7)	2.5 (2.0)	0.5
Dosage forms of HTN drugs, n (%)					0.04
Single	425 (70.4)	104 (62.7)	133 (73.5)	188 (73.2)	
Fixed-dose combination	179 (29.6)	62 (37.3)	48 (26.5)	69 (26.8)	
Side effects of HTN drugs, n (%)					0.61
Yes	71 (11.8)	16 (9.6)	23 (12.7)	32 (12.5)	
None	533 (88.2)	150 (90.4)	158 (87.3)	225 (87.5)	
No. of medication sources, n (%)					0.04
1	534 (88.4)	149 (89.8)	167 (92.3)	218 (84.8)	
≥ 2	70 (11.6)	17 (10.2)	14 (7.7)	39 (15.2)	
No. of complications, n (%)					0.92
1	279 (46.2)	78 (47.0)	86 (47.5)	115 (44.7)	
2	97 (16.1)	30 (18.1)	25 (13.8)	42 (16.3)	
≥ 3	24 (3.9)	5 (3.0)	8 (4.4)	11 (4.3)	
None	204 (33.8)	53 (31.9)	62 (34.3)	89 (34.6)	
Duration of HTN, mean (SD)	10.8 (9.9)	12.0 (10.2)	11.8 (11.9)	9.4 (7.8)	0.01
No. of CAM, n (%)					0.66
1	156 (25.8)	44 (26.5)	50 (27.6)	62 (24.1)	
≥ 2	15 (2.5)	2 (1.2)	6 (3.3)	7 (2.7)	
None	433 (71.7)	120 (72.3)	125 (69.1)	188 (73.2)	

SD: Standard Deviation; HTN: Hypertension; CAM: Complementary and Alternative Medicine

of participants were female; 39.9% had graduated from elementary school; 70.9% were married; 86.8% were living with their families; 55.6% had a middle financial status; and 69.0% were unemployed. The mean adherence score was 5.4 (SD=2.4). The low adherence group (42.5%) accounted for most participants, followed by the medium adherence (30.0%) and the high adherence (27.5%) groups. Among the demographic variables, only age, education status, marital status and employment status (P <0.05 for all) showed significant differences between the three groups. Bonferroni's post hoc tests revealed a significant difference between the high and low adherence groups and between the medium and low adherence groups with respect to age (P<0.05).

Table 2 presents details of medication regimens and medical history of participants. The overall mean number of prescribed medications and pills were 4.9 (SD=2.6) and 7.8 (SD=5.4), respectively. The mean number of different antihypertensive drugs administered simultaneously, and the mean number of total pills prescribed per participant were 1.6 (SD=0.8) and 2.3 (SD=1.4), respectively. The mean daily frequency of medication was 2.5 (SD=1.9); 70.4% of patients were prescribed a single form of medication, and 11.8% patients experienced side effects of medications. Approximately 46.2% of the participants had one complication and 88.4% had a single source of medication. The average duration of HTN was 10.8 (SD=9.9) years. Only 28.3% participants used a CAM for HTN, while 2.5% participants used ≥ 2 CAM. Significant differences were observed between the three groups with respect to dosage forms of antihypertensive drugs, number of sources of medications and the duration of hypertension (P<0.05 for all). No significant between-group differences were observed with respect to medication for other conditions and medical history. Bonferroni's post hoc test indicated a significant difference between the high and low adherence groups and between the medium and low adherence groups with respect to the duration of hypertension (P<0.05).

Table 3 presents BP values of participants. There were significant differences among the three groups with regard to SBP, DBP and MAP (P<0.05 for all). Bonferroni's post hoc tests indicated significant differences between the high and low adherence groups and between the medium and low adherence groups with respect to DBP and MAP (P<0.05 for each), but not SBP.

All demographic variables and variables related to medical history are potential confounding factors that may affect medication adherence. On multivariate regression analysis, medication regimen variables were found to have a significant effect on medication adherence after adjusting for demographic and medical history-related variables. R2 value was 0.10, which indicated that medication regimen-related variables accounted for 10% of the variance in adherence. Multiple sources of medication were found to have a

Table 3: Blood pressure values disaggregated by level of adherence to antihypertensive therapy.

Variables	All (n=604)	High (n=166)	Medium (n=181)	Low (n=257)	*P*
SBP, mean (SD), mmHg	138.4 (15.7)	137.1 (15.5)	136.8 (14.7)	140.2 (16.3)	0.04
DBP, mean (SD), mmHg	81.1 (9.3)	79.8 (7.9)	80.2 (9.3)	82.5 (10.0)	0.01
MAP, mean (SD), mmHg	100.2 (10.2)	98.9 (9.2)	99.1 (9.7)	101.8 (10.9)	<0.01

SD: Standard Deviation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure

Table 4: Results of MLR model predicting blood pressure values.

		SBP			DBP			MAP	
Variables	β[a]	SE	*P*	β[a]	SE	*P*	β[a]	SE	*P*
Adherence (score)	-0.60	0.27	0.03	-0.32	0.16	0.04	-0.41	0.17	0.02
Age (years)	0.15	0.07	0.03	-0.12	0.04	<0.01	-0.03	0.04	0.49
Gender	1.28	1.45	0.38	-0.28	0.83	0.74	0.24	0.93	0.8
Education	-0.99	0.57	0.08	0.02	0.33	0.94	-0.32	0.37	0.39
Marital status	0.89	0.91	0.33	0.62	0.52	0.24	0.71	0.58	0.23
Residence	-0.33	1.46	0.82	-1.39	0.84	0.1	-1.03	0.94	0.27
Financial status	-0.02	1.03	0.99	0.26	0.59	0.66	0.17	0.66	0.8
Employment	-1.45	0.88	0.1	-1.64	0.51	<0.01	-1.58	0.57	0.01
Alcohol intake	2.14	2.17	0.32	2.83	1.24	0.02	2.6	1.39	0.06
Smoking	-1.00	2.06	0.63	-1.09	1.17	0.36	-1.06	1.32	0.42
Betel nut chewing	3.67	2.21	0.1	0.92	1.26	0.47	1.84	1.41	0.19
Regular exercise	1.64	1.38	0.24	0.42	0.79	0.6	0.83	0.88	0.35
Sleeping status	1.83	0.82	0.03	-.19	0.47	0.68	0.48	0.53	0.36
Diet	1.19	1.4	0.4	1.17	0.8	0.14	1.17	0.89	0.19
Stress	0.04	0.21	0.84	<0.01	0.12	0.98	0.02	0.13	0.91
Obesity (BMI: kg/m²)	0.38	0.15	0.01	0.26	0.09	<0.01	0.3	0.1	<0.01
Self-management BP	-0.52	0.33	0.12	0.02	0.19	0.93	-0.16	0.21	0.44
CAM	-1.07	1.24	0.39	-0.21	0.71	0.77	-0.50	0.8	0.53
DDI	3.23	2.19	0.14	1.87	1.25	0.14	2.33	1.4	0.1

[a]unstandardised β , $R^2_{non\text{-}adj}$ was 0.10, 0.15, and 0.10 for SBP, DBP and MAP
MLR: Multivariate Linear Regression; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; BMI: Body Mass Index; CAM: Complementary and Alternative Medicine; DDI: Drug-Drug Interaction

significant effect on adherence (P<0.05). Increase in the number of sources of medication was significantly associated with decrease in adherence (β= -1.06, P<0.01); in addition, a single source of medication was associated with significantly higher adherence as compared to ≥ 2 sources of medications.

All health-related behaviors, CAM and DDI variables are potential confounding factors that may affect the BP outcome. In the MLR model, adherence level was found to predict the BP level after adjusting for health behavior, CAM and DDI variables. R2 values for this model were 0.10, 0.15 and 0.10, indicating that adherence accounted for 10%, 15% and 10% of the variance in SBP, DBP and MAP (Table 4). Adherence was a predictor of SBP (β= -0.60, P=0.03), DBP (β= -0.32, P=0.04) and MAP (β= -0.41, P=0.02).

Discussion

There are two major findings of this cross-sectional study. First, multiple sources of medications have a significant impact on medication adherence, which was found to increase with decrease in the number of medications. Second, medication adherence was found to predict the BP level after controlling for potential confounding factors. Non-adherence direct caused poor control of BP.

Hypertension is a chronic medical condition, and the average duration of hypertension in our study population was 11 years [21]. In a cohort study by Caro et al. [31], the persistence of established hypertensive patients (97%) is higher than newly-diagnosed hypertensive patients (78%). Bane et al. [32] reported that social-cognition also has a significant influence on medication adherence. The multiple sources of medications may produce medication regimen complexity, including dosage forms, drug type, and pill count and dosage frequency. For these reasons, multiple sources of medications may play an important role in reducing adherence to antihypertensive therapy.

Non-adherence to medication is related to several factors including demographic, medication regimen, medical history and social-cognition variables, including age, gender, socioeconomic level, number of drugs, dosage frequency, dosage forms, side effects, number of prescribing physicians, complications, disease duration and self-efficacy [2,4-6,14,15,32-35]. Here, we also observed significant differences between different adherence groups with respect to age, education status, marital status, and employment status, number of sources of medications, dosage forms and duration of hypertension.

In our study, the SBP, DBP and MAP values decreased with

increase in medication adherence of participants. In other words, the SBP, DBP and MAP in the high adherence group were lower than those in the medium and low adherence groups. These findings are consistent with previous reports which showed that medication adherence is directly associated with control of BP [2,34,35]. Therefore, good adherence direct caused good control of BP.

Our study highlights several characteristics of hypertensive patients in Taiwan. The low adherence group accounted for 42.5% of the total study population; therefore, the adherence rate in this study (high plus medium adherence) was 57.5%. The mean number of medications and pills prescribed were 4.9 and 7.8, respectively. The mean number of antihypertensive drugs and pills prescribed per participant were 1.6 and 2.3, respectively. The mean administration frequency of medication was 2.5% and 70.4 percentage points of the participants were prescribed a single form of medication; 11.8% of the study population experienced side effects associated with antihypertensive therapy. Approximately 46.2% of the participants had experienced one complication and 88.4% of the patients had a single source of medication.

Our present study has its limitation. Although the questionnaire is a reliable, valid, efficient and cost-effective tool, it may lead to remarkable overestimation of adherence in a cross sectional study since it would measure subjective judgment of patients in answering the questionnaire [31]. The most widely applied method is questionnaire which tends to overestimate the actual medication adherence [31]. In an effort to avoid overestimation of adherence, the conditions for adherence are strictly measured, following physician's instructions and never skip any pill. Using questionnaire may be acceptable for a prospective study. Additional strengths of this study are that (1) the participants are highly representative of the Taiwan's east population, since the regional hospital, in religious principle, receives patients from all socioeconomic classes, and (2) based in part on data from the hospital electronic record system and each patient's chart.

Conclusion and Implications for Research and/or Practice

This study assessed medication adherence among hypertensive patients during the calendar year 2010 using the medication adherence questionnaire. There are several interesting findings in the study. The number of sources of medication had a significant effect on medication adherence; a single source of medication was associated with significantly higher adherence as compared to multiple sources of medications. The level of adherence showed a direct association with the level of BP control.

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Disclosures

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