

Proportion and risk indicators of nonadherence to antihypertensive therapy: a meta-analysis

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Purpose: The World Health Organization (WHO) concluded that poor adherence to treatment is the most important cause of uncontrolled high blood pressure, with approximately 75% of patients not achieving optimum blood pressure control. The WHO estimates that between 20% and 80% of patients receiving treatment for hypertension are adherent. As such, the first objective of our study was to quantify the proportion of nonadherence to antihypertensive therapy in real-world observational study settings. The second objective was to provide estimates of independent risk indicators associated with nonadherence to antihypertensive therapy.

Materials and methods: We performed a systematic literature review and meta-analysis of all studies published between database inception and December 31, 2011 that reviewed adherence, and risk indicators associated with nonadherence, to antihypertensive medications.

Results: In the end, 26 studies met our inclusion and exclusion criteria and passed our methodological quality evaluation. Of the 26 studies, 48.5% (95% confidence interval 47.7%–49.2%) of patients were adherent to antihypertensive medications at 1 year of follow-up. The associations between 114 variables and nonadherence to antihypertensive medications were reviewed. After meta-analysis, nine variables were associated with nonadherence to antihypertensive medications: diuretics in comparison to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs), ACE inhibitors in comparison to ARBs, CCBs in comparison to ARBs, those with depression or using antidepressants, not having diabetes, lower income status, and minority cultural status.

Conclusion: This study clarifies the extent of adherence along with determining nine independent risk indicators associated with nonadherence to antihypertensive medications.

Keywords: meta-analysis, antihypertensives, adherence

Introduction

In a comprehensive report on nonadherence to long term therapies, the World Health Organization (WHO) stated that treatment of hypertension can reduce the risk of stroke by 30%–43% and myocardial infarction by 15%, along with reducing the risk of a number of other chronic conditions.¹ Similarly, in a meta-analysis of 147 randomized trials, the authors found that patients who received treatment with antihypertensive medications observed a 22% reduction in coronary heart disease events and a 41% reduction in stroke.² However, the WHO also concluded that poor adherence to treatment is the most important cause of uncontrolled high blood pressure, with approximately 75% of patients not achieving optimum blood pressure control.¹ The implications are vast. A meta-analysis on interventions for enhancing medication adherence completed by the Cochrane Collaboration concluded that effective ways to help patients follow medical

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treatments could have far larger effects on health outcomes than any individual treatment by itself.³ For example, one review estimated that better adherence to antihypertensive therapy could prevent 89,000 premature deaths in the US alone on an annual basis.⁴

In a meta-analysis on proportion and risk indicators for statin therapy, the authors found that only 49% of patients are adherent in real-world observational studies. After reviewing 147 variables, only six covariates were found to be independently associated with nonadherence to statin therapy: primary prevention, new statin users, copayment, lower income status, fewer than two lipid tests performed, and not having a comorbidity of hypertension.⁵

To date, a systematic literature review and meta-analysis has not been performed on the extent of nonadherence to antihypertensive therapy. As such, the WHO had to estimate that between 20%–80% of patients receiving treatment for hypertension are adherent.¹ In other words, the true extent of nonadherence is not known and is a justification for this review.

The WHO also concluded that there is an urgent need for research to fill gaps in knowledge on the determinants of adherence.¹ Two systematic reviews have been published on variables associated with nonadherence to antihypertensive therapy. The first reviewed the impact of depression, but included self-report adherence information.⁶ The second reviewed differences in adherence between angiotensin receptor blockers (ARBs) and other antihypertensive drug classes. However, the authors used filters to limit the search strategy and excluded studies that used a single point in time (ie, 1 year) to define adherence.⁷ As well, both studies modified established quality-assessment rating checklists for their quality review.^{6,7}

The first objective of our study was to quantify the proportion of adherence to antihypertensive therapy in real-world observational study settings. The second objective was to provide estimates of independent risk indicators associated with nonadherence to antihypertensive therapy.

Materials and methods

We performed a systematic literature review of electronic databases: Medline (Ovid), Embase (Ovid), International Pharmaceutical Abstracts (Ovid), the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Sociological Abstracts (ProQuest), ProQuest Dissertations and Theses, Theses Canada, and OAIster from inception to December 31, 2011. Multiple combinations of search terms and keywords were used to

maximize the ability to capture relevant articles. Papers that were not published electronically were not included in our search. Reference sections of each article were reviewed for additional papers (Figure 1).

Studies were included if they satisfied the following criteria: 1) nonadherence to antihypertensive medications as an outcome, 2) antihypertensive medications included angiotensin-converting enzyme inhibitors (ACEIs), ARBs, beta blockers, calcium channel blockers (CCBs), or thiazide diuretics for any indication, 3) dispensation records as the source of objective nonadherence information, 4) conducted multivariable modeling to determine the independent effect of covariates on the outcome of nonadherence, and 5) published in the English language.

Abstracts and full-text articles were assessed by two reviewers for relevance (MWA and ML). Study quality was reviewed with a checklist developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for database studies. The checklist was developed for the specific purpose of critically evaluating the unique complexity of administrative datasets analyzing medication adherence.^{8,9} This checklist has been used in other systematic reviews.¹⁰ It consists of 27 quality-review questions related to data source, research design, study population, variable definitions, statistics, and discussion. We established a rule a priori that studies scoring 14/27 or higher (greater than 50%) on the quality checklist would be included in the meta-analysis, unless there was a major methodological violation.

Disagreement between the two reviewers was resolved by additional review and discussion, and then, if required, with the senior author (ML) making a final decision. We assessed agreement between reviewers with κ -statistics.¹¹

We conducted a random-effects model meta-analysis using the inverse-variance method to estimate the effect of a risk indicator on medication adherence. A random-effects model accounts for potential heterogeneity between the populations and unmeasured confounding.^{12–15} Given that rates of adherence were being compared, rate ratios (RRs) were computed instead of odds ratios. Four or more articles were required for meta-analysis.

Sensitivity analysis reviewed the individual influence of a study by repeating the meta-analysis without studies with the largest and smallest relative weights. If this produced little change in inference (less than 15% change in rate ratio), inclusion of the study would not warrant caution in the interpretation. Sensitivity analysis also included country of origin and measures used to calculate adherence. We used the *Z*-test for overall effects and the χ^2 statistic to test for differences

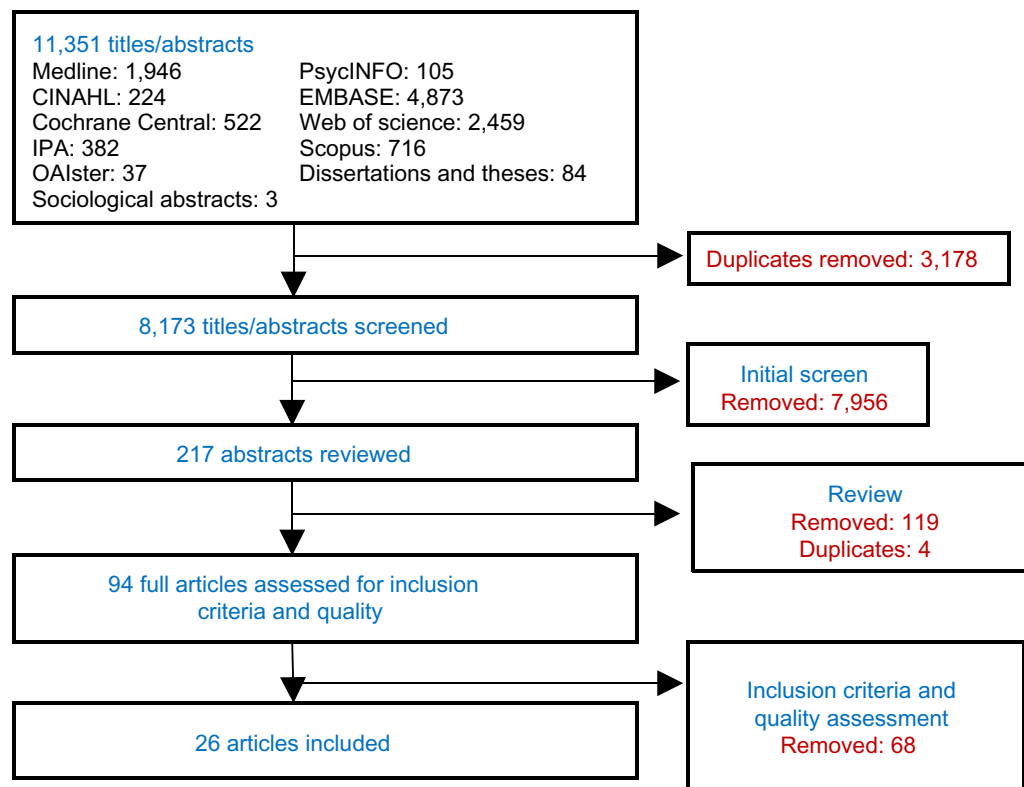


Figure 1 Systematic literature-review process.

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health; IPA, International Pharmaceutical Abstracts; OAlster, Open Archives Initiative.

in between-group effects. We included every risk indicator tested in other studies, but we obviously have no information on indicators that were not tested.

Results

A total of 11,351 titles and abstracts were identified. After review, and after removing duplicates, 217 abstracts were considered relevant to our study. From these, 94 articles were relevant, reviewed in full and evaluated for quality with the ISPOR checklist.^{8,9} Of these 94 articles, 26 passed the methodological quality review¹⁶⁻⁴¹ (Figure 1). The κ -statistic for agreement between the reviewers for the final articles was 0.73. Even among approved studies, the methodological quality was low, with an average score of 16.8 out of a maximum of 27.

Of the 26 studies included for analysis, the most common follow-up duration was 12 months, for which 17 studies and 20 cohorts had data. Among these, with a total sample size of 1,522,203, 48.5% (95% confidence interval [CI] 47.7%–49.2%) of patients were adherent to antihypertensive medications at 1 year of follow-up, with a range from 20% to 88%. One study had a sample size of 725,220, which contributed 47.6% of the total sample. Removal of this one large study resulted in an adherence level of 56.9% (95% CI

56.7%–57.1%). This paper was also the only study conducted outside of North America and Europe with follow-up duration of 12 months. The two most common adherence measures were proportion of days covered and discontinuation, with adherence levels of 62.2% (95% CI 61.9%–62.5%) for proportion of days covered and 55.1% (95% CI 55.0%–55.2%) for discontinuation.

The second objective was to provide estimates of risk indicators associated with nonadherence to antihypertensive therapy. In total, the associations between 114 variables and nonadherence to antihypertensive medications were reviewed. In the end, nine variables were associated with nonadherence to antihypertensive medications, with five representing drug class and four from variables other than drug class (Table 1 and Figure 2).

For five studies and seven cohorts with a total sample size of 1,082,417, patients who were dispensed diuretics, in comparison to ACEIs, were 36% more likely to be non-adherent (RR 1.36, 95% CI 1.22–1.51). Among five studies and seven cohorts with a total sample size of 1,028,044, patients who were dispensed diuretics, in comparison to ARBs, were 47% more likely to be nonadherent (RR 1.47, 95% CI 1.27–1.70). For three studies and five cohorts with a total sample size of 295,512, patients who were dispensed

Table 1 Results of individual studies

	Rate ratio	95% CI	Relative weight	Homogeneity
ACEIs versus ARBs				
Bloom ¹⁹	1.19	1.03–1.32	0.26	
Elliott et al ²³	1.14	1.09–1.20	0.28	
Wogen et al ³³	1.45	1.43–1.47	0.29	
Degli Esposti et al ³⁶	1.58	1.12–2.08	0.16	
Pooled	1.30	1.10–1.54	1.00	0.000
CCBs versus ARBs				
Sung et al ³⁸	1.10	1.09–1.11	0.29	
Elliott et al ²³	1.32	1.26–1.39	0.28	
Wogen et al ³³	1.33	1.31–1.35	0.29	
Degli Esposti et al ³⁶	2.07	1.57–2.73	0.14	
Pooled	1.33	1.16–1.54	1.00	0.000
Diuretics versus ACEIs				
Elliott et al ²³	1.53	1.47–1.61	0.14	
Taira et al ²⁵	1.49	1.40–1.60	0.14	
Van Wijk et al ²⁶	1.52	1.46–1.57	0.14	
Van Wijk et al ²⁶	1.32	1.28–1.36	0.15	
Van Wijk et al ²⁶	1.38	1.33–1.43	0.14	
Friedman et al ³⁰	1.17	1.10–1.25	0.14	
Sung et al ³⁸	1.16	1.14–1.17	0.15	
Pooled	1.36	1.22–1.51	1.00	0.000
Diuretics versus ARBs				
Degli Esposti et al ³⁶	2.62	1.99–3.46	0.10	
Taira et al ²⁵	1.61	1.50–1.70	0.15	
Van Wijk et al ²⁶	1.50	1.42–1.57	0.15	
Van Wijk et al ²⁶	1.45	1.31–1.56	0.15	
Van Wijk et al ²⁶	1.52	1.47–1.56	0.15	
Friedman et al ³⁰	1.07	0.93–1.22	0.14	
Sung et al ³⁸	1.16	1.14–1.17	0.15	
Pooled	1.47	1.27–1.70	1.00	0.000
Diuretics versus CCBs				
Friedman et al ³⁰	1.08	0.99–1.19	0.19	
Taira et al ²⁵	2.01	1.90–2.20	0.20	
Van Wijk et al ²⁶	1.46	1.35–1.53	0.20	
Van Wijk et al ²⁶	1.15	1.06–1.22	0.20	
Van Wijk et al ²⁶	1.23	1.16–1.29	0.20	
Pooled	1.35	1.14–1.60	1.00	0.000
Depression versus no depression				
Rasmussen et al ¹⁶	2.13	1.44–3.14	0.02	
Rasmussen et al ¹⁶	1.81	1.07–3.07	0.01	
Perreault et al ²⁴	0.93	0.85–1.02	0.14	
Van Wijk et al ²⁶	1.10	0.99–1.14	0.19	
Van Wijk et al ²⁶	1.14	1.05–1.25	0.14	
Van Wijk et al ²⁶	1.03	0.94–1.12	0.15	
Siegel et al ²⁹	1.16	1.14–1.18	0.20	
Evans et al ³⁹	1.17	1.09–1.26	0.16	
Pooled	1.11	1.05–1.18	1.00	0.000
Low income versus higher				
Rasmussen et al ¹⁶	1.05	0.91–1.11	0.09	
Rasmussen et al ¹⁶	1.07	0.94–1.23	0.06	
Perreault et al ²⁴	1.34	1.26–1.42	0.09	
Van Wijk et al ²⁶	0.94	0.86–1.02	0.08	
Van Wijk et al ²⁶	1.19	1.15–1.23	0.09	
Van Wijk et al ²⁶	1.05	1.01–1.10	0.09	
Gogovor et al ²⁸	1.02	0.83–1.26	0.04	
Gogovor et al ²⁸	1.26	1.11–1.42	0.06	

(Continued)

Table 1 (Continued)

	Rate ratio	95% CI	Relative weight	Homogeneity
Friedman et al ³⁰	1.10	1.08–1.12	0.10	
Corrao et al ³¹	1.02	0.98–1.05	0.09	
Wong et al ³⁷	1.22	1.15–1.29	0.09	
Evans et al ³⁹	1.60	1.31–1.96	0.04	
Rasmussen et al ⁴⁰	0.98	0.90–1.14	0.09	
Pooled	1.12	1.06–1.18	1.00	0.000
Diabetics versus nondiabetics				
Rasmussen et al ¹⁶	0.98	0.68–1.22	0.03	
Rasmussen et al ¹⁶	1.16	0.85–1.38	0.02	
Setoguchi et al ¹⁷	1.03	1.00–1.06	0.12	
Setoguchi et al ¹⁷	1.03	0.99–1.06	0.11	
Degli Esposti et al ²⁰	0.50	0.17–0.76	0.04	
Perreault et al ²⁴	1.14	1.06–1.21	0.09	
Taira et al ²⁵	1.13	1.10–1.20	0.12	
Van Wijk et al ²⁶	1.01	0.92–1.09	0.09	
Van Wijk et al ²⁶	1.03	1.00–1.14	0.09	
Van Wijk et al ²⁶	1.17	1.10–1.24	0.09	
Gogovor et al ²⁸	1.11	0.92–1.27	0.04	
Gogovor et al ²⁸	1.19	1.07–1.29	0.06	
Siegel et al ²⁹	1.02	0.99–1.04	0.12	
Pooled	1.07	1.02–1.11	1.00	0.000
Black versus White				
Setoguchi et al ¹⁷	1.23	1.19–1.27	0.15	
Setoguchi et al ¹⁷	1.09	1.06–1.13	0.15	
Yang et al ²¹	1.38	1.36–1.39	0.15	
Shaya et al ²²	1.55	1.30–1.71	0.13	
Van Wijk et al ²⁶	1.42	1.19–1.66	0.11	
Siegel et al ²⁹	1.08	1.07–1.09	0.15	
Yang et al ²¹	1.28	1.27–1.30	0.15	
Pooled	1.27	1.14–1.42	1.00	0.000

Abbreviations: CI, confidence interval; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

diuretics, in comparison to CCBs, were 35% more likely to be nonadherent (RR 1.35, 95% CI 1.14–1.60). Pooling of four studies with a total sample size of 232,665 revealed that patients who were dispensed ACEIs, in comparison to ARBs, were 30% more likely to be nonadherent (RR 1.30, 95% CI 1.10–1.54). Analysis of four studies with a total sample size of 936,162 showed that patients who were dispensed CCBs, in comparison to ARBs, were 33% more likely to be nonadherent (RR 1.33, 95% CI 1.16–1.54).

There were five studies and eight cohorts that reviewed the association between depression or the use of antidepressants and nonadherence. With a total sample size of 206,673, patients who were either depressed or dispensed antidepressants were 11% more likely to be nonadherent to antihypertensive medications (RR 1.11, 95% CI 1.05–1.18).

Comparing lowest-income to highest-income groups among nine studies and 13 cohorts with a sample size of 623,444, we found that lower-income groups were 12% more likely to be nonadherent (RR 1.12, 95% CI 1.06–1.18).

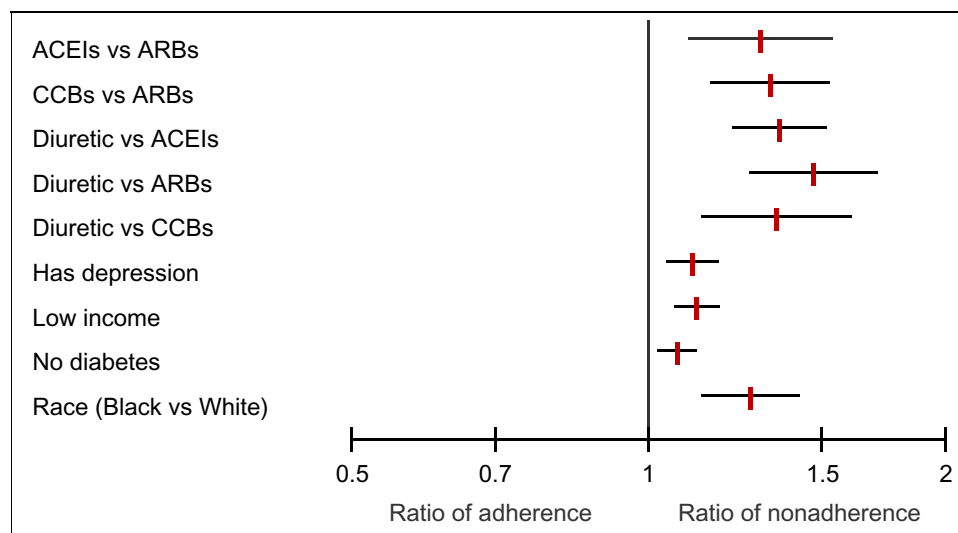


Figure 2 Covariates independently associated with nonadherence to antihypertensives.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

Some studies reviewed race. Analysis of five studies and seven cohorts with a sample size of 1,771,428 revealed that residents who were of minority cultural status (African American race in American studies) in comparison to Caucasian (White) were 27% more likely to be nonadherent (RR 1.27, 95% CI 1.14–1.42).

There were eight studies and 13 cohorts that reviewed the association between having diabetes and nonadherence. With a total sample size of 252,306, patients without diabetes were 7% more likely to be nonadherent to antihypertensive medications (RR 1.07, 95% CI 1.02–1.11).

There was no known association between the other 105 variables and nonadherence to antihypertensive medications. For example, patients with ischemic heart disease were only 3% more likely to be nonadherent to antihypertensive medications (RR 1.03, 95% CI 0.90–1.18). As another example, patients with heart failure were 5% more likely to be nonadherent to antihypertensive medications (RR 1.05, 95% CI 0.98–1.12).⁴²

Tests of homogeneity of variance for the nine variables associated with nonadherence were all $P < 0.001$. This suggests highly significant heterogeneity between the studies. Stratification by country of origin and measure of adherence did not alter estimates to a significant degree. As well, sensitivity analysis of removing studies with the largest and smallest relative weights did not alter estimates to a significant degree. For example, removing non-North American and -European studies and removing the study with the largest sample size modified the odds ratio between diuretics and ACEIs from 1.36 (95% CI 1.22–1.51) to 1.40 (95% CI 1.24–1.56).

Only three variables had negative estimates or results contrary to the other studies in the meta-analysis. Among eight cohorts that reviewed the association between depression or the use of antidepressants and nonadherence, one estimate was inconsistent with the other seven. For the thirteen cohorts that reviewed income, two estimates were inconsistent with the other eleven estimates. Among thirteen cohorts that reviewed the association between diabetes and nonadherence, two estimates were inconsistent with the other eleven.

All of the included papers are summarized in detail in [Table S1](#).

Discussion

Of the 26 studies that were included in our study and passed methodological quality review, 48.5% (95% CI 47.7%–49.2%) of patients were adherent to antihypertensive medications at 1 year of follow-up. This clarifies the original WHO estimate that between 20% and 80% of patients receiving treatment for hypertension are adherent.¹ This is simply a range from the lowest to the highest rates found during their review. Policy makers and health practitioners could assume that nonadherence is as low as 20% and therefore not a major problem. We quantified the value through meta-analysis in order to clarify the need for action.

Our study also provides estimates of known risk indicators associated with nonadherence to antihypertensive therapy. In total, the associations between 114 variables and nonadherence to antihypertensive medications were reviewed. In the end, nine variables were associated with

nonadherence to antihypertensive medications: diuretics in comparison to ACEIs and ARBs and CCBs, ACEIs in comparison to ARBs, CCBs in comparison to ARBs, those with depression or using antidepressants, not having diabetes, lower income status, and minority cultural status (African American race).

Although drug class has been shown to impact adherence, it is not clear if this is due to the properties of the drug class itself. One review suggests that differences may be due to patient selection or that out-of-pocket cost predicts drug choice.⁷ Also, the reality is that many patients are now started on more than one antihypertensive medication and combinations of drug classes.⁷ A recent paper found that differences in adherence by drug class were associated with their market availability, and that combination therapy of ARBs with diuretics had the highest proportion of adherence.⁴³ Others would suggest that there are clinical differences like increased urination associated with diuretics.⁴⁴ Regardless, our results were consistent with a meta-analysis that reviewed adherence of ARBs in comparison to other antihypertensive medications, although our study reviewed all drug classes.⁷

Depression is known to be associated with a threefold-greater risk of nonadherence to medical treatment in general.⁴⁵ A previous systematic literature review found that definitive conclusions could not be drawn between depression and nonadherence to antihypertensive therapy, possibly because five of the eight accepted studies included nonobjective and self-report measures to determine nonadherence.⁶ Our review addressed this limitation.

Not having diabetes was also associated with nonadherence, although the effect was small. Patients who have a low perceived risk of disease have been found less likely to adhere to their medications.⁵ Lower-income status might also increase nonadherence due to affordability, although low-income status has also been associated with nonadherence to other health-seeking behaviors.^{46–49} The association between cultural status and adherence is likely to be due to confounding with income.⁵⁰ In the US, African American cultural status is well known to be more likely associated with lower-income status at the population level.⁵¹

The main limitation of our meta-analysis was the inclusion of studies with wide variability and heterogeneity in measuring and defining adherence. Second, although our meta-analysis identified nine variables associated with nonadherence to antihypertensive medications, it remains unclear as to what extent adherence would be improved if these variables were addressed. Third, our interpretation is limited to variables reviewed. It is likely that other untested associations exist.

Conclusion

The known effectiveness of interventions for enhancing chronic disease medication adherence remains surprisingly weak.³ It is possible that this lack of effectiveness is due to not really knowing the risk indicators of nonadherence. This study provides some insight into factors associated, and not associated, with nonadherence to antihypertensive medications.

In summary, it is likely that effective ways to help patients follow medical treatments could have far larger effects on health outcomes than any individual treatment. The first step is to know the extent of nonadherence in patients and populations. The second is to have some idea as to what variables are associated with nonadherence.

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