Promoting Persistence: Improving Adherence Through Choice of Drug Class

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Editorial

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Medication nonadherence is a public health epidemic. Numerous studies evaluating a wide variety of drugs and conducted in varied healthcare settings have described the consistent nature of this problem.[1] Hypertension is no exception: Almost half of patients become nonadherent to their antihypertensive medication within 1 year of initiating therapy.[2] Although difficult to quantify precisely,[3] the consequences of nonadherence are significant: preventable death, disability, and health spending.

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The complexity of therapeutic regimens, treatment side effects, cognitive impairment, misperceptions of the benefits or risks of treatment, poor provider–patient relationships, cost, and difficulties accessing physicians or pharmacies all influence the ability of patients to take their medications as prescribed.[4–6] Accordingly, drugs or drug classes that differ on these or other influential characteristics may reasonably be expected to have different rates of long-term adherence. Antihypertensives are a good example: angiotensin-converting enzyme (ACE) inhibitors are most likely to cause cough, angiotensin receptor blockers (ARBs) are the most expensive, and physicians and patients may perceive diuretics to be least effective,[7] despite high-quality data to the contrary.

To evaluate this further, Kronish et al systematically reviewed and pooled results from observational studies comparing adherence, defined primarily as persistence, or the number of days from treatment initiation to complete discontinuation, across antihypertensive classes. The included studies consistently found adherence to be highest among those prescribed ARBs and lowest among diuretic users.[8] The overall magnitude of these differences are striking. Angiotensin receptor blocker– and ACE inhibitor–treated patients appear 75% to 100% more adherent than those receiving diuretics.

Although these results are intriguing, we should interpret this meta-analysis with caution. There is substantial statistical heterogeneity between the included studies that remained explained in sensitivity analyses; thus, the combined effect estimates may be inaccurate. Publication bias and industry funding appear to be playing a role, and, when accounted for, substantially reduced the apparent advantage of ARBs over ACE inhibitors. Perhaps most importantly, the analysis relied on data from observational studies. These data sources have notable advantages: They provide the opportunity to evaluate populations who are frequently excluded from trials, situations where monitoring and follow-up are not intensive, and outcomes that are relatively rare. However, they may also have important biases, which if inadequately handled can lead to incorrect and potentially misleading inferences.

In the real world, therapeutic choices are rarely made randomly. Physicians attempt to tailor blood pressure treatments to the specific circumstances of their patients. Age, sex, comorbid conditions, insurance status, and the characteristics of the drugs themselves are common considerations, and many of the studies included in meta-analysis by Kronish et al adjusted for these and other potential confounders. However, there are numerous other factors influencing medication use that are difficult to distinguish from nonpersistence, especially when using claims data, but that have substantially different implications for quality improvement efforts. For example, rather than discontinuing treatment on their own, patients may have stopped their ACE inhibitors as directed by a physician because of bothersome cough or refractory hyperkalemia. Because this would generally result in patients being switched to another drug class rather than stopping therapy altogether, assessing adherence to any antihypertensive medication and not just to the specific medication class on which they were initiated might result in much smaller differences in adherence between classes. In fact, when the authors evaluated this outcome instead, the differences in adherence between ARB and ACE inhibitors were no longer significant.

Healthy user effects may have also influenced the results. Patients often differ in the degree to which they engage in healthy behaviors, such as the use of preventive services. These differences are not surprisingly also associated with higher rates of medication adherence.[9] If no attempts were made to address these characteristics, then the apparent association between medication class and adherence may actually be due to confounding by health seeking, even in analyses that use multivariable models to carefully adjust for observable covariates. Said another way, although the differences in adherence may well reflect what drug classes patients received, they may also be influenced by who received them. The magnitude of the apparent associations, a doubling of the hazard of nonadherence for diuretics as

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compared with ARBs, makes this type of residual confounding a real possibility.

Nevertheless, if the results by Kronish et al are even partially true they call into question the advantages of diuretics found in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[10] and may thus have important therapeutic implications. This landmark 33 357-person randomized study of hypertensive patients with at least 1 cardiac risk factor found rates of coronary heart disease death or nonfatal myocardial infarction, the study's primary outcome, to not differ between those receiving chlorthalidone, lisinopril, or amlodipine. In the trial, chlorthalidone users were most like to have continued to receive their assigned therapy, which may be considered a proxy for adherence. If the situation were reversed (ie, adherence was lowest for chlorthalidone), then outcomes among calcium-channel blocker– and ACE inhibitor–treated patients may well have been superior to those of their diuretic-treated counterparts. Further, the 20% to 40% reduction in the risk of incident heart failure from diuretics, which has been a key contributor to recommendations supporting these agents as first-line for hypertension, could be substantially smaller, and potentially clinically irrelevant, when factoring in adherence.

Of course, the extent to which the therapeutic advantages of diuretics are diminished by nonpersistence is a matter of speculation, as are the implications for population health of preferentially initiating antihypertensive therapy with an ARB. At equipotent doses, the major antihypertensive classes all appear to have similar effects on blood pressure lowering and rates of major cardiovascular events,[11] but the evidence base evaluating the comparative effectiveness of ARBs for clinically relevant outcomes is substantially more limited.[12] Further, with the exception of losartan, which recently became available as a generic medication, ARBs in North America and Europe are only sold as brand-name agents and do not appear on any of the $4 generics lists offered by many large US pharmacies.[13] Increasing ARB use may thus have significant consequences for overall health system spending.[14] For patients, out-of-pocket costs have consistently been linked to higher rates of nonadherence even among well insured individuals.[15] In fact, in contrast to the suggestion otherwise by Kronish et al, the only 2 studies included in their review that specifically evaluated copayments both demonstrate significantly lower rates of adherence with higher cost sharing across and within drug classes.[16,17] For example, Zhang et al found that a $10 increase in copayments increased a patient's odds of nonpersistence by >30%. This may certainly diminish the apparent adherence advantage of ARBs.

Notwithstanding their limitations, the provocative results of Kronish et al's study have validity and highlight the importance of considering long-term use from the outset of therapy. Perhaps the most indisputable finding from this study is that adherence to all hypertensive classes is suboptimal. Even for ARB users, rates of nonpersistence were >35%. Adequately addressing this public health problem is a complex task and truly requires a systems-based approach,[5,18] but practicing clinicians have a vital role to play. First, as part of routine practice, we must ask patients about adherence and difficulties they may have had taking their medications as prescribed. As with other efforts to change patient behavior, such as smoking cessation, physician engagement and close follow-up appear to substantially reduce gaps in therapy.[19] Second, we must consider factors like dosing complexity and cost in our therapeutic decision making. Substituting medications with simpler dosing schedules (eg, an ACE inhibitor that is dosed once daily instead of 2 or 3 times daily) or using agents that are therapeutically equivalent but lower cost (ie, generics or brand-name medications that have preferred status on a patient's formulary) may help patients adhere to their prescribed therapies.[20] Third, we should remind patients about expected and often transient side effects, like the diuretic action of thiazides, that may lead them to unnecessarily stop therapy. Perhaps, most important of all, we must be vigilant regardless of which class of drugs we prescribe. Promoting persistence should be a public health priority.

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