Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): An Example for Observing Early Guideline Adoption Patterns

It has been estimated that it takes an average of 17 years for new knowledge to be integrated into clinical practice. The trajectory of this adoption is still inconsistent. The rapidity of integration may depend on the ease of changing the current practice, the importance of integration and other factors, such as insurance coverage (which may lag in some cases). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) offers a useful case study in examining knowledge adoption.

An abundance of evidence demonstrates that medications are not only effective in treating hypertension, but also that they considerably reduce hypertension-associated morbidity and mortality. Consequently, we have seen a proliferation of new antihypertensive agents (AAs) during the last 20 years. Standard antihypertensive therapies, such as diuretics (the so-called “water pills”), have been joined by more expensive medications, including α-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). Before publication of ALLHAT, little comparative data existed to help clinicians select the most appropriate therapeutic approach for hypertensive patients.

Researchers at Jefferson Medical College and University of Utah sought to examine the effect of the ALLHAT recommendations on physicians prescribing behavior changes.

**Did Italian Physicians Change their Antihypertensive Prescribing after Publication of the ALLHAT Results?**

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Begun in February 1994 and completed in March 2002, ALLHAT is the largest prospective hypertension trial ever conducted, and was intended to compare effectiveness among available AAs to provide physicians with evidence-based recommendations. In March 2000, the α-blocker
arm of ALLHAT was prematurely discontinued because of a greater risk of cardiovascular
events as compared to diuretics. In December 2002, the ALLHAT findings were published,
recommending that thiazide-type diuretics (THZD) be used for first-step therapy in
uncomplicated hypertensive patients. The ALLHAT results have been widely disseminated in
journal publications and even in news releases. However, it remains to be seen whether, and to
what extent, physician prescribing behavior for AAs has changed as a result of the new clinical
evidence. In general, evidence from clinical trials and practice guidelines has a limited impact on
physician behavior.

Recent trend analyses on consumption of AAs conducted in the United States and Canada show
that physicians have, to some extent, responded to the new clinical evidence of ALLHAT,
prescribing significantly more diuretics and fewer ACEs, CCBs, and α-blockers for their
patients. Thus far, no information on the impact of the ALLHAT results has been available in
Europe, where physician prescribing attitudes may be influenced substantially by cultural
factors, as well as specific pharmaceutical policies. Using a comprehensive automated outpatient
pharmacy database in Emilia Romagna, a northern Italian Region with a population of 4 million,
we investigated trends in AA prescribing following the publication of the ALLHAT results. This
research has been jointly conducted by the Center for Research in Medical Education and Health
Care and the Department of Health Policy, both at Jefferson Medical College, supported through
a collaborative agreement with the Agenzia Sanitaria Regionale, Regione Emilia Romagna, Italy.

We examined outpatient pharmacy claims of all Emilia Romagna residents from 2000 through
2003 and computed the monthly total number and relative percentages of prescriptions for
THZDs, ACEs or ARBs, CCBs, β-blockers, α-blockers, and other-type antihypertensive
diuretics. Combinations of these antihypertensive classes were not included in the analysis
because they accounted for small percentages of the total number of AA prescriptions. We
performed a time series analysis using a stepwise auto-regressive forecasting model, and then
assessed the impact of the ALLHAT recommendations on use of each antihypertensive class by
calculating predicted relative percentages and 95% confidence intervals for each of the 12
months of 2003.

During the study period, ACEs/ARBs and CCBs represented the largest relative percentages of
AA prescriptions (approximately 40 percent and 30 percent, respectively), while the relative
percentages for other-type antihypertensive diuretics and β-blockers were roughly 12 percent and
10 percent, respectively. Alpha-blockers and THZDs accounted for approximately 4 percent and
1 percent of all AA prescriptions, respectively. Use of THZDs and ACEs/ARBs showed an
overall upward trend, which was not statistically significantly different than that predicted by the
time-series model in the 12 months, following publication of the ALLHAT findings. The relative
percentage of CCBs diminished over time, but was significantly higher than predicted in the last
4 months of 2003. The percentage of β-blockers was stable overall, as were the percentages of α-
blockers and other-type antihypertensive diuretics.

This analysis provides evidence that the ALLHAT findings had limited impact on the prescribing
patterns of antihypertensive drugs in Emilia Romagna. Further research is needed to investigate
why Italian physicians appear unresponsive to the new clinical evidence. Educational programs
and implementation of pay-for-performance strategies may be warranted to influence physician prescribing behavior to improve the quality of care for hypertensive patients.

**And How about U.S. Physician Antihypertensive Prescribing after Publication of the ALLHAT Results?**

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In a similar study, the University of Utah Pharmacotherapy Outcomes Research Center sought to answer the same question among U.S. physicians using a national electronic medical record (EMR) primary care practice database, which contains ambulatory health record data for over 3.2 million individuals. This retrospective study evaluated AA utilization among hypertensive patients in the year before and after publication of ALLHAT results. Subjects for this analysis were identified in calendar years 2002 and 2003 as patients 18 years and older with an ICD-9 code (401.xx) for hypertension and a generic product index (GPI) code for any of the following 5 classes of AAs (excluding combinations): β-blockers, ACEs, CCBs, THZDs, and ARBs. Patients were grouped into one of five AA classes according to the first prescription they received after diagnosis of hypertension.

Quartile analysis was used to compare the rates of patients on each of the five classes of AAs for the four quarters of both 2002 and 2003. We found a statistically significant 3.9 percent increase in the proportion of patients on THZDs for 2003 compared to 2002. We also found a statistically significant decrease in the rate of patients on ACEs (2.9 percent), β-blockers (1.3 percent), and CCBs (0.5 percent), and a statistically significant increase in the rate of patients on ARBs (0.9 percent). Although the increase in THZD use was modest, it supports the notion that the
ALLHAT findings had some effect on prescribing behavior. It remains to be seen, however, whether such prescribing trends would be maintained long-term.

**Conclusion**

The results of these two studies show that the ALLHAT recommendations have had a modest influence, if any, on physician prescribing behaviors for AAs in two countries. However, we also recognize that these analyses examined data immediately following the release of the recommendations in late 2002; these modest changes reflect ordering behaviors of the early adopters or integrators of the information. While these analyses corroborate existing data in the literature that physicians are somewhat slow, or even reluctant, to embrace new clinical evidence, similar analyses examining prescribing behaviors 5 or 6 years after the recommendations may continue to show uptake and offer more insights into information adoption. We urge that professional medical associations and organizations worldwide begin designing, implementing, and evaluating strategies for more effective and rapid dissemination of relevant results from clinical trials among their constituents.

9. Maio V, Yuen EJ, Smith KD, Louis DZ. Prescribing patterns following publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial