The Final Translational Hurdle

Transforming Trial Results Into Practice Change

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The connection between clinical research and typical patient care presents a frustrating paradox. Many well-documented advances in therapy are not adopted widely or quickly, whereas other, unimpressive new treatments are taken up in epidemic proportions, their use often fueled by marketing campaigns that are far more powerful than the medicines being advertised. As a result, patients are frequently exposed to new therapies that may be less effective or less safe than the older regimens they replace. For example, ezetimibe (Zetia and Vytorin; Merck/Sharpe-Plough Pharmaceuticals, North Wales, Pennsylvania) may not prevent atherosclerosis as well as the statin-only regimens it displaces for many patients; rosiglitazone maleate (Avandia; GlaxoSmithKline, Philadelphia, Pennsylvania) increases the risk of cardiovascular disease in patients with diabetes mellitus; and rofecoxib (Vioxx; Merck & Co Inc, Whitehouse Station, New Jersey) nearly doubled the occurrence of myocardial infarction or stroke in patients who took it, while offering no greater analgesic efficacy than older nonsteroidal anti-inflammatory drugs, such as naproxen sodium. The lavish promotion that drives such overuse is reserved for the most expensive drugs, because use of thiazides was often the very habit that nor the persistence of clinicians’ old habits of care—should guide therapy but does not. The treatment of hypertension is a striking example of this problem. During the late 1980s and 1990s, it seemed as if the more trial evidence that was published documenting the efficacy of thiazide-type diuretics in treating blood pressure, the smaller the market share of these drugs became. The problem was not the adequacy or relevance of these trials, nor the persistence of clinicians’ old habits of care—because use of thiazides was often the very habit that was being displaced. Nor was it the failure of the scientific community to enunciate clear, evidence-based recommendations about therapy, as represented by the JNC7. Rather, it was the growing dominance of marketing-based communication suggesting that these drugs were “old-fashioned” and should be displaced by the more “modern” treatments of CCBs and ACE inhibitors as initial therapy for patients with uncomplicated hypertension. Changes in hypertension treatment during these years provide compelling evidence of the power of commercially driven research and promotion to drive practice.

Despite the recent upsurge of interest in translational research—moving a basic science discovery from the laboratory to drug development and evaluation—far less attention has been paid to the final translational hurdle: ensuring that the results of well-conducted clinical research are applied to typical patient care. This is the important agenda that Stafford et al have attempted to address in their article.
The ALLHAT study was a milestone in several respects. Before comparative effectiveness research was a hot new (and temporarily well funded) research trend, the ALLHAT investigators took on a question that came up literally hundreds of thousands of times each day in physician-patient encounters all over the world: What is the best initial treatment for a patient with uncomplicated hypertension? For this condition as for many others, the US Food and Drug Administration (FDA) often grants approval for a new medication based on its capacity to improve a surrogate marker (in this case, blood pressure) when compared with placebo. In the absence of systematic follow-up studies, this proliferation of many “better than nothing” drugs left practitioners without clear guidance about how each agent really compared with the others. When ALLHAT demonstrated that for these patients with hypertension but no major comorbidities, thiazide-type diuretics were as good as or better than other agents that at the time were considerably more costly, many hoped this “old-fashioned” approach would gain new respect and credibility. Yet, publication of this landmark study resulted in a surprisingly small change in patterns of care.

Why was the uptake of ALLHAT so modest, and why did the ALLHAT/JNC7 Dissemination Project described herein not itself have greater impact? As late as 2002, many observers of the health care system, like many economists, still held a simple “rational actor” view of how people make decisions. According to this perspective, individuals seek out the best available evidence for several possible choices, weigh each, determine the most rational course of action, and carry it out. (This naive view has traditionally been taken more seriously by policymakers and academics than by those who actually work on the front lines in clinical care or commerce.) While there were important methodological issues related to the ALLHAT study design, its main findings were clear, robust, and plausible...case closed, right?

Alas, trial results do not transform practitioners’ decisions any more than pills leap out of their containers and into patients’ gastrointestinal tracts. Like medications, research findings need adequate delivery systems and must be accompanied by appropriate behavioral interventions if they are to have any effect. Unfortunately, most clinical trials are not designed with this in mind. Consideration of how the ALLHAT findings would be adopted did not anticipate that its implementation could threaten hundreds of millions of dollars in revenue generated by the still-patented medications that the study found to be generally no better than a thiazide-type regimen. A concerted backlash followed, based in part on some plausible clinical and methodological concerns, but probably more so by an enthusiastic campaign of ALLHAT bashing.

Addressing such barriers has traditionally not been considered part of the mandate of the National Institutes of Health (NIH). Until very recently, many argued that the NIH is charged with identifying and funding the best biomedical research but is not responsible for how that research is or is not implemented. Supporters of this traditionalist view of the NIH mission have long resisted using its resources to support such “applied” work at all. This view is analogous to the orthodox view of the FDA as an agency engaged only in the approval of new drugs, with no responsibility for how physicians use those drugs in practice. As the director of the NHLBI, Claude Lenfant, MD, signaled a change in this attitude in a seminal 2003 article. Fortunately, both the FDA and NIH have recently begun to acknowledge that they also need to engage with how the health care system integrates the research and regulatory decisions (respectively) for which each organization is responsible.

The ALLHAT investigators, as well as the NHLBI, which funded the trial and its follow-up implementation project, are to be commended for considering the impact of their study and—noting its modest effect—taking the next step to launch an innovative program to disseminate those results to a poorly responsive audience of clinicians. The good news is that this initiative took place, and that it seems to have achieved a small change in practice. But why so small?

The most important reason for the modest effect size reported by Stafford et al is that although the authors describe the intervention as “academic detailing,” it really was not. (Readers will perhaps excuse such a bald assertion coming from the person who invented the process and gave it that name in the first article on this topic in 1983.) The ALLHAT dissemination program did attempt to bring its message to physicians in a less-passive-than-usual educational program. But the single most important reason that academic detailing programs work is that they are modeled on one “special ingredient” central to the pharmaceutical sales activities the approach is named for: the interactive, one-on-one presentation of a message to a practicing clinician by an experienced change agent. Pharmaceutical companies spend billions of dollars on their in-office promotional activities because they know that the single best way to persuade someone to change behavior is to engage that person in a dialogue. These conversations enable a talented communicator to understand the physician’s current practices, beliefs, and attitudes, making it possible to tailor a behavior-change message specifically to that individual’s decision-making process. This is why such an approach changes practice far better than typical didactic lectures, which have been shown to accomplish this goal poorly. An interactive conversation also actively engages the learner’s participation in the information exchange: a physician is far less likely to tune out or doze off during a conversation than at a typical grand rounds presentation. The efficacy of this interactive form of educational outreach was well documented in additional randomized trials in the early years of its development and has since been reassessed in a rigorous review of the literature conducted by the Cochrane Collaborative, which confirmed its effectiveness in an analysis of 69 controlled trials of the intervention. Programs based on this approach are now in place in several parts of the United States as well as elsewhere around the world.

Budget limitations probably prevented the ALLHAT/JNC7 Dissemination Project from performing real academic detailing. Instead, it resorted to far less effective group presentations, many of which probably degenerated (in a behavior-change sense) to conventional talk-at-you lectures. It is therefore not surprising that its impact on changing practice was so modest.

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Several other methodological issues in pharmacoepidemiology may also secondarily explain the small effect size reported in the current article. First, the data available to the investigators could not separate new starts of antihypertensive therapy from continuing regimens. The need for a “new user” design is becoming well established in observational drug safety studies and has an added relevance here. In this case, even if a physician became convinced of the ALLHAT conclusions, understandable clinical inertia may well have made prescribers reluctant to apply these recommendations to change the regimens of established patients with hypertension who were doing well. Instead, they would have been more likely to implement its findings in newly diagnosed patients treated de novo. However, the investigators were limited to data on all patients taking antihypertensive drugs, most of whom would have been “prevalent users” rather than new starts. This inability to separate veterans from virgins would have obscured any effect the program might have had on influencing new prescribing decisions.

Nonetheless, Stafford et al, the ALLHAT team, and the NHLBI infrastructure that made all this possible deserve praise for taking up this difficult but immensely important challenge. The field of translational research is a new one, and addressing the final rate-limiting step of bringing research findings into the mainstream of typical practice represents one of its most difficult challenges. Workers in this thorny field now recognize several key insights that were less well understood when ALLHAT was conceived, conducted, and reported. First, important findings cannot be expected to implement themselves, however well conceived and executed a clinical trial may be. Second, addressing such implementation is a legitimate responsibility of the biomedical enterprise. “Implementation science” is a crucial, underemphasized, but growing aspect of medical practice.22

If the clinical research enterprise works as well as it should, potentially practice-changing trials will be completed with increasing frequency. As soon as it is clear that a study has produced findings that will require widespread implementation to improve patients’ health, a coordinated program should be initiated to bring those findings to practitioners (and perhaps to patients), in a salient way that will change behavior and improve outcomes. This may involve new prompts embedded into electronic medical records, dissemination of the findings through new or existing academic detailing programs, public awareness campaigns, and updating of quality-assurance measures. Discovering the truth in and of itself will not be enough to ensure that the public will benefit from these discoveries. This agenda will become particularly important with the growth of comparative effectiveness research. Performed well, these studies will yield numerous findings about what works best that will be of limited use if they are not translated into everyday clinical decisionmaking.

Our prescribed regimens of drugs, procedures, and diagnostic tests are becoming ever more effective, powerful, and costly. Developing the knowledge base and delivery systems to transform these findings into improved decision making on the front lines of patient care must become an increasingly central part of the research enterprise, as well as of the health care delivery system itself.

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