By Jerry Avorn and Michael Fischer

'Bench To Behavior': Translating Comparative Effectiveness Research Into Improved Clinical Practice

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ABSTRACT **The new national emphasis on comparative effectiveness research is likely to generate an unprecedented volume of new findings. It is essential to anticipate the obstacles that front-line health care professionals will face in translating these results into better clinical decision making. We review the current barriers to the dissemination of evidence-based clinical recommendations, including problems with continuing medical education, provider incentives, and quality assurance. We then propose solutions, including more effective educational outreach programs, requirements for practitioners to master important findings, and alignment of incentives to encourage evidence-based practice. Such strategies can lead to policies that could encourage the uptake of new comparative effectiveness data and encourage their translation into better clinical practice.**

Jerry Avorn (javorn@medsoc.harvard.edu), an internist and drug epidemiologist, is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, at Brigham and Women's Hospital, in Boston, Massachusetts.

Michael Fischer is a health services researcher and primary care physician in the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, at Brigham and Women's Hospital. He also is an assistant professor of medicine at Harvard Medical School.

The industrialized world has focused intensely in recent decades on applying advances in basic biomedical research to the production of new drugs and devices. However, this "bench to bedside" translation has not been matched by comparable attention to using that research to change what physicians actually do—what might be called the "bench to behavior" translation. A major gap persists between the best available information on therapeutic effectiveness and safety, on the one hand, and typical patterns of care, on the other.[1,2] Problems in translating into practice the conclusions of several major comparative effectiveness research trials, as discussed below, show that studies may be rigorously designed and carried out, producing important clinical findings, yet remain poorly applied in typical practice settings.

Emergence Of New Research Findings

As a result of recent changes in federal law, new funding, and the creation of the new Patient-Centered Outcomes Research Institute, the United States is now gearing up to produce an unprecedented volume of new research evaluating comparable therapeutic interventions. It is critical to understand the barriers that exist between generating these comparative effectiveness findings and changing practice by front-line physicians and other health professionals—and to develop strategies to overcome these obstacles.[3]

Delaying the adoption of research findings—or refusing to adopt them—is not a novel problem in medicine. In the mid-nineteenth century, Ignác Semmelweis in Europe and Oliver Wendell Holmes Sr. in the United States employed observational and then interventional "comparative effectiveness" studies to demonstrate that hand washing by health professionals before they delivered babies was associated with a marked reduction in maternal death from puerperal fever, a serious bacterial infection that can affect mothers after childbirth. Yet it took the medical profession years to incorporate these life-saving

insights into standard practice.[4]

In 1992, Elliott M. Antman and colleagues demonstrated the long lag between documenting effective advances in heart disease care and incorporating those findings into expert review articles and textbook chapters. In addition to documenting the translation-to-practice problem clearly, they also pointed out that clinical experts themselves often contributed to delays in the inclusion of important new findings into standard texts and reviews.[5] Antman and colleagues suspected that even experts struggled to find and evaluate all of the new evidence in a given clinical area.

The nature of the problem has not changed. With increasingly powerful and costly treatments coming onto the market, and with the expected avalanche of new comparative effective research, we need to overcome these long-standing barriers to translating results into practice, to make certain that these new insights are applied appropriately.

Flawed Underlying Assumptions

Many biomedical researchers assume that as soon as new information that can improve the quality or cost-effectiveness of care is published in the medical literature, it will be noticed and promptly adopted by clinicians and policy makers. This could be called the "If you discover it, they will come" philosophy. Although enormous effort and expense are devoted to conceiving and implementing a carefully wrought clinical trial, there is often no plan for putting its results into practice once it is finished.

It is difficult to think of an example of a major biomedical discovery in which this passive posture alone has been followed by adequate practice change. Vaccination against polio, the concept that mild-to-moderate hypertension requires treatment, the use of statins to prevent cardiovascular events, the administration of antibiotics near the time of surgery—all are interventions for which having clear evidence in the medical literature was not adequate in itself to consistently transform practice on a large scale.

A laissez-faire approach to adopting effective care improvements can result in both under- and overuse of the studied intervention. One example is the enormous investment in multiple studies of the comparative effectiveness of antiplatelet regimens with and without clopidogrel (Plavix) to reduce the risk of cardiovascular events. Despite this investment, Niteesh Choudhry and colleagues recently found that in almost half of the cases in one large, state-funded program in which this costly medication was given to patients, there was no apparent indication that its use was necessary.[6]

Below we review the barriers to the implementation of insights from comparative effectiveness research in routine clinical practice. We also propose ways of overcoming the barriers to help move comparative research findings from the pages of medical journals into typical patient care settings.

Causes Of The Problem

NO EFFECTIVE DISSEMINATION The evolution of the clinical trial has focused attention on a number of its critical components. These include rigorous calculation of the necessary sample size and the need for human subjects protection, safety monitoring boards, and accurate and appropriate statistical analysis.[7] Despite these important advances, most clinical trial designs do not yet include a plan for getting the study's findings translated into the world of patient care.

Research results can also have unintended adverse consequences if they are misapplied. An example is the Randomized Spironolactone Evaluation Study (RALES), which demonstrated the advantage of adding spironolactone (a diuretic) to the drug regimens of patients with severe heart failure.[8] However, use of spironolactone in patients older and frailer than those included in the clinical trial produced a strikingly higher rate of dangerous side effects.[9]

The problem of underapplication of research findings dogged a project funded by the National Institutes of Health, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Known as ALLHAT, this was a landmark comparative effectiveness study of more than 40,000 patients with hypertension, in which subjects were randomly assigned to four drug regimens.

Contrary to the expectations of many experts, the trial demonstrated that older thiazide-type diuretic drugs, available in generic versions, were as effective as or better than three other heavily marketed competing regimens.[10] This created an opportunity for substantial improvement in the treatment of hypertension, with better care at lower cost.[11]

However, publication of the ALLHAT hypertension findings had only a brief, modest effect on prescribing.[12] The reasons included the initial absence of a dissemination plan for the findings; effective countermarketing by the manufacturers of the threatened products; and criticism of the study—some of it justified—by several hypertension experts.[13] An important next step was taken when the National Heart, Lung, and Blood Institute funded an implementation and dis-

semination program to encourage incorporation of the landmark study's results into practice.[14] Unfortunately, the program's impact was small, probably because it used conventional educational approaches such as lectures, which have been shown to have limited effectiveness in changing behavior.[15]

A similar problem characterizes many comprehensive programs to review comparative evidence about medications or other technologies. The reviews are typically extremely thorough, but the resulting documents are so long and detailed that they often fail to influence—or even get read by—most practitioners. The Agency for Healthcare Research and Quality (AHRQ), which funds many such evidence reviews, has recently begun to address this issue by developing updated versions of these reviews[16] and seeking improved methods of dissemination (see discussion of academic detailing below).

CONTINUING MEDICAL EDUCATION One likely avenue for the dissemination of future comparative effectiveness research will be continuing medical education programs for physicians and other health professionals. However, such programs are of uneven quality, and many of them are supported by companies that produce the products being discussed.[17] Manufacturers of drugs and devices underwrite tens of thousands of these activities each year, at an annual cost of well over $1 billion,[18,19] either directly or through so-called medical educational companies. These companies are also often largely supported by the manufacturers, which calls the companies' independence into question. Pfizer's decision in 2008 to stop such indirect funding of continuing medical education programs may indicate a coming change in this model.[20]

Additional education that appears to present comparative data about alternative therapeutic choices comes to practitioners via industry-funded speakers' bureaus of physicians. These doctors are typically paid by a manufacturer to give lectures about the company's products, often complete with text and slides provided by the drug maker. Companies argue that the content of these lectures must be strictly defined by them to comply with Food and Drug Administration (FDA) regulations because the speakers are functioning as a marketing arm of the manufacturer. Such pressure to deliver a message consistent with the sponsor's needs can lead to a distorted presentation of comparative effectiveness findings.[21]

In fact, some continuing medical education actually de-educates prescribers by emphasizing material supporting the use of a costly brand-name product, even if the bulk of comparative research does not favor it.

OFFICIAL MARKETING PROGRAMS Sometimes, a new drug or device will be found to be meaningfully better than an existing competitor, and this information is successfully disseminated by the manufacturer of the superior product. This kind of marketing can be useful.

More often, however, manufacturers' marketing presents clinical decision makers and patients with messages that favor the use of more expensive options regardless of any demonstrated clinical advantage. This dynamic is often driven by the fact that only these products can earn enough money to support costly promotional campaigns. A recent review of all medication-related papers published in six major journals found that comparative studies were more likely than other papers to have been funded by government rather than industry sources,[22] but industry has generally done a more effective job than the public sector in communicating study results.

In addition to advertising, pharmaceutical sales representatives—known as detailers—are a frequent source of comparative drug information for most physicians. Many doctors meet with several such representatives each week.[23] Beyond the sometimes skewed nature of the comparative data presented, these encounters in the past have created an opportunity for the representatives to promote off-label prescribing, even in the absence of evidence supporting it.[24]

Forceful marketing is consistent with companies' fiduciary responsibility to their shareholders to maximize return on their investment, but it often does not disseminate the messages that are most consistent with comparative effectiveness research. In recent years, the US Department of Justice has aggressively investigated charges of companies' fraudulent off-label marketing of prescription drug products. This has resulted in settlements of billions of dollars, some of the largest penalties in US corporate history.

New leadership at the FDA may be more forceful about monitoring poorly substantiated claims of superiority over competing medications. It remains to be seen how these developments will affect the content of company-sponsored promotional statements in the future.

▶ **HYPERTENSION DRUGS:** The capacity of promotion to counteract comparative effectiveness findings is illustrated by the example of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) for the treatment of hypertension. Both ACE inhibitors and ARBs work through similar mechanisms. Comparative effectiveness trials have shown that both are equally effective in the vast majority of

cases at lowering blood pressure,[25] increasing survival, and achieving other important clinical outcomes.[26–29]

Many low-cost generic ACE inhibitors are available, while the newer ARBs are only now beginning to face generic competition. Thus, ARBs have been marketed heavily, while there is very little promotion of most generic ACE inhibitors.

Thus, ARBs have been among the fastest-growing drugs used to treat hypertension. Enormous sums are spent on these heavily advertised medications, which offer no clinical advantage to most patients, thereby driving up expenditures for programs such as Medicaid, Medicare, and private insurers, as well as patients.[30]

▶ **ANTIDEPRESSANT DRUGS:** Antidepressant drugs provide another example. When the antidepressant citalopram (brand name Celexa) was losing its patent protection, its manufacturer obtained FDA approval to market escitalopram, named Lexapro, the drug's L-isomer—which had essentially the same molecular structure.

Studies comparing the new drug to its older sibling found only a trivial difference in depression scores for patients treated with escitalopram.[31] Moreover, comparisons of escitalopram to other antidepressants did not show improved outcomes.[32,33] Nevertheless, heavy marketing of Lexapro has continued, yielding sales of $2.3 billion in 2008, despite the availability of much less expensive and equally effective alternatives.[34]

▶ **HEART FAILURE DRUGS:** The cardiac drug Natrecor (nesiritide) provides a somewhat different lesson. This intravenous medication was approved on the basis of studies in specific subpopulations of patients with severe heart failure. The studies initially seemed to indicate the medication's superiority over competing regimens. But when Natrecor was heavily promoted for use in a broader population of patients, adverse effects increased markedly. The drug's manufacturer was forced to issue a new guideline suggesting that Natrecor be used only with the most severely ill heart failure patients.[35] Additional experience with the drug has raised worrisome questions about its safety, such as the risk of renal toxicity or increased mortality.

In this case, the problem was not the absence of an implementation plan. Rather, an overzealous marketing plan encouraged the use of the drug beyond the patient population for which it was originally approved.

PHYSICIAN RESISTANCE Some translational barriers to the implementation of comparative effectiveness results are deeply entrenched in the financing system of health care in most US settings. Physicians who earn much of their income by performing a given procedure are unlikely to implement the results of a study that found the procedure to be no better than a less costly or safer alternative.

For example, the Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) comparative effectiveness trial evaluated whether coronary angioplasty to unblock clogged coronary arteries increased survival compared to aggressive drug treatment alone. Released in 2007, the study found no difference in rates of death or major cardiovascular events in patients who were randomly assigned to undergo angioplasty compared to those treated with drugs.[36]

Although the study raised important questions about the limits of invasive cardiologic procedures compared to more conservative approaches,[36] it did not have a major impact on patterns of care. Three years later, cardiologists continue to perform many angioplasties, despite evidence that for many patients, the procedure offers little additional benefit than other less invasive—and far less costly—treatments.[37]

Comparative effectiveness research methods are increasingly applied to diagnostic procedures, and the results of such evaluations are often similarly ignored by the clinicians who depend on such procedures for their livelihood. Computed tomography (CT) of the coronary arteries has been promoted as a means of visualizing atherosclerotic plaques and calcifications.[38] But when the test was evaluated rigorously against established alternatives, it was found to offer little advantage over current angiographic approaches,[39] while increasing a patient's exposure to radiation.[40]

Nevertheless, the test remains popular with clinicians. An attempt by the Center for Medicare and Medicaid Services (CMS) to stop paying for computed tomography was met with strong resistance by radiologists. Ultimately, CMS reversed itself and continued to pay for the procedure.[41]

In such situations, education alone will not ensure the adoption of results from comparative effectiveness research. This insight was anticipated by Upton Sinclair, who observed, "It is difficult to get a man to understand something when his salary depends on his not understanding it."[42]

Another source of physician resistance is conceptual rather than economic. Ever since the term *evidence-based medicine* was introduced by David L. Sackett, Gordon H. Guyatt, and their colleagues,[43] some clinicians have objected to the approach, arguing that such data-driven recommendations could miss the idiosyncratic ways in which a disease—or a treatment—may operate in

particular patients. Critics have also argued that different patients may have different preferences that are not adequately taken into account by recommendations for what works best "on average."

ABSENCE OF QUALITY CONTROL In most practice settings, physicians' clinical decisions are not subjected to any formal quality review. As a result, making use of even the most important findings from comparative effectiveness research remains at the discretion of the practitioner.

Pay-for-performance models aim to tie compensation to desired behavior. But developing appropriate metrics for assessing performance has proved problematic, and it is not clear how well strategies currently under consideration would promote and reward use of research findings and improve the quality of clinical care, especially for patients with multiple medical conditions.[44,45]

Physician report cards have been suggested as another possible way to encourage more evidence-based practice, and in theory they could promote more decision making based on comparative effectiveness research. Advocates of this approach suggest that making data on physician practice patterns or outcomes available to the public would pressure physicians who provide less evidence-based care to improve their decision making.

However, early studies of such report cards have found that the measurements used were not easily understood by the public and may not have reflected the actual quality of care.[46,47] At least one study found that report cards may have actually led to worse outcomes for patients.[48]

Some Possible Solutions

This brief review of some of the barriers to translating the results of comparative effectiveness research into improved care suggests several points of intervention that are worth considering. The relatively new field known as implementation science is a source of both encouragement and anxiety in this regard.[49,50]

Implementation science provides encouragement because it has taught us a good deal in the past decade about what works in transforming scientific advances into changed practice. It is also a source of anxiety because it has shown that barriers to this transformation process are higher than had been realized, and many promising interventions have not worked very well. For instance, rapid response teams for prompt assessment of hospital inpatients at risk for transfer to intensive care showed promise in improving patient outcomes when first studied.[51] However, reviews of attempts to implement rapid response teams in other hospitals and settings did not demonstrate a consistent benefit.[52]

EARLY PLANNING FOR DISSEMINATION The designers of comparative effectiveness research studies that could meaningfully transform practice should routinely consider at the outset how the studies' findings could be disseminated and incorporated into practice. Such planning should consider the clinician groups to whom messages will be targeted, as well as how to reach relevant patient populations. Specific messages and plans for changing practice can be developed once a study's findings are known and can be produced as soon as the final results are published. As this dissemination planning becomes a more prominent part of clinical trial design, researchers will naturally turn their attention to the most effective means of dissemination, as described below.

IMPROVEMENT OF PRACTITIONER EDUCATION Growing skepticism over corporate-funded continuing medical education will lead to a more receptive audience for unbiased, evidence-based findings in the coming years. Three major organizations—the Josiah Macy Jr. Foundation,[19] the Association of American Medical Colleges,[53] and the Institute of Medicine[54]—have recently issued reports critical of industry's role in continuing medical education. Each advocated an end to sponsorship of these activities by drug or device manufacturers, and each argued against participation of academic medical center faculty in speakers' bureaus or other promotional activities.

As the environment changes, there may be a window of opportunity to develop new models of continuing medical education, focused on publicizing the best available evidence instead of on marketing products.

▶ **ACADEMIC DETAILING:** Programs of noncommercial educational outreach are becoming more widely available as a tool for translating the results of important comparative effectiveness studies into routine care. Many such programs use the concept of academic detailing, which is based on the observation that the pharmaceutical industry has been far more effective than the academic community in transmitting its messages and translating them into physician behavior change.

Academic sources usually provide more-neutral, evidence-based information about comparative therapeutic choices, but they tend to present their material to practitioners in a conventional didactic format, such as a lecture, and in a centralized location. In contrast, academic detailing offers educational outreach visits to

physicians in their offices—like the visits of drug company sales representatives—ensuring better penetration of the market or audience than centralized continuing medical education courses can achieve.

In addition, academic detailing allows communication to be tailored to the individual recipient, which is a big advantage in adult learning. Engaging the participant in discussion is also a more effective means of transmitting a message and increasing the likelihood that it will lead to changed behavior.

Initial studies demonstrated that academic detailing could improve prescribing for a variety of purposes, including pain control, the treatment of common infections, and the use of sedating drugs in the elderly.[55,56] More recent studies have analyzed academic detailing in a wide variety of settings. A 2007 Cochrane review analyzed sixty-nine trials of such educational outreach, involving more than 15,000 health professionals. The review concluded that the literature proved the efficacy of this approach and that these interventions can lead to important improvements in prescribing.[57]

Academic detailing programs are now in place in several states[58] and integrated health systems, as well as in other countries such as Australia and Canada. AHRQ has recently made funds available so that national programs can use such outreach approaches to further the integration of comparative evidence-based recommendations into practice.[59,60]

▶ **HEALTH INFORMATION TECHNOLOGY:** Computerized physician order entry has long been seen as a promising tool to help providers implement comparative effectiveness research findings in their practice. In principle, incorporating the findings into order entry systems should be a cost-effective and efficient means of bringing this information to the attention of clinicians at key "teachable moments" during patient care.

The benefits of such computerized interventions have been demonstrated primarily in inpatient hospital settings; evidence in routine outpatient settings has been more limited.[61] Recent studies have demonstrated that targeted interventions in outpatient electronic prescribing systems can change specific elements of prescribing behavior.[62,63] However, there is also evidence that computer-assisted prompts do not always work as well as expected in terms of either quality improvement or cost containment.[64–66]

Another potential set of problems lies in the content of such messages. Fueled by a major infusion of federal funds, the speed of expansion of electronic order entry systems may initially be accompanied by inadequate attention to the validity and source of the clinical decision prompts that the software delivers. This is likely to become a contentious area as such systems become more common.

In any case, the proliferation of electronic health records will ensure that computerized order entry guidance will become much more widespread. Considerably more research will be needed to determine the optimal content of the messages, and how such systems can best be integrated into health care delivery to maximize their usefulness in applying comparative effectiveness research findings in clinical decision making.[67]

LIMITING PROBLEMATIC PROMOTIONAL MESSAGES The incentive structure for manufacturers of drugs and devices is likely to continue to favor behavior that leads to maximum sales. Manufacturers' sales and their promotional messages to clinicians and patients will continue to be a major factor in shaping what doctors and consumers know about the effectiveness and safety of these products. But much can be done to make the messages better reflect the totality of comparative effectiveness evidence.

Given the power of the FDA to regulate such communications, the agency could impose stronger requirements that promotional material addressed to both prescribers and patients include data on relevant comparisons with alternative treatment options. The agency could also require more-accurate presentations of the relative benefits and risks of the products being promoted. Finally, the FDA has the power to ban claims—direct or implied—of superiority that are not substantiated by the bulk of the evidence.

ADDRESSING PHYSICIAN RESISTANCE With the proliferation of medical informatics, it is becoming increasingly possible to assess to what degree a clinician's practice is evidence based—in other words, how often clinical decisions match the best available recommendations for care. To the extent that differences between providers in this regard are economically driven, one attractive option is to move toward methods that pay physicians based on how well their clinical decisions match "ideal" care, as defined by comparative effectiveness data.

For example, cardiologists and radiologists would be rewarded for performing coronary interventions or magnetic resonance imaging (MRI) studies on patients for whom those procedures are indicated, according to evidence-based guidelines. Similarly, those physicians would be penalized for doing either too many or too few of the procedures.

However, the mixed track record of current pay-for-performance experiments indicates that much more work is needed before this approach

is ready for wide application. Particular care must be taken to ensure that any incentive-based system places a premium on making the most appropriate clinical decisions, instead of the least expensive ones.

Physician resistance that is cognitively, rather than economically, based raises a completely different set of issues. Successive definitions of evidence-based medicine by Sackett, Guyatt, and their colleagues came to include the concepts of physician judgment and patient preference as filters of pure evidence.[68,69] The insights of genetics also play a role now, as one explanation for the often-heard—and sometimes valid—objection, "This patient is different."

Considerable work will be needed in the coming years to define when actual variations in a patient's genetics, physiology, or values truly warrant a departure from using a given treatment that has been shown to work best in larger populations. Sometimes that departure will be wise. But on other occasions, appeals to individual differences in the absence of supporting data may merely be smokescreens for opposition to any kind of decision making that places greater weight on evidence than on subjectivity.

QUALITY CONTROL FOR EVIDENCE-BASED PRACTICE In addition to the questionable nature of some continuing education content, there is generally no requirement that physicians demonstrate that they have actually learned any of the material presented in these programs. Recently, however, many specialties have begun to require physicians to demonstrate continued proficiency to maintain board certification. Basic familiarity with current comparative effectiveness data could be made a criterion for recertification.

However, physicians who do not choose to become recertified still deliver a large amount of health care in the United States. A more effective way of increasing the application of comparative effectiveness findings would be to require as a precondition for licensure renewal, hospital credentialing, or reimbursement by payers that a practitioner demonstrate his or her grasp of current data on what works best in common clinical situations.

Conclusion

We need much more research to better understand the current barriers to translating the findings of comparative effectiveness research into clinical practice. We also need a clearer understanding of which approaches to translation work best, which have only a modest impact, and which may even be counterproductive in certain situations.

Substantial energy and resources will be devoted to pursuing a vigorous program of comparative effectiveness research. The results of that work must be communicated to physicians and other health care professionals and actually put to use by them, to improve the quality and affordability of health care. The unattractive alternative is that the nation's ambitious research agenda will simply add to the long list of medical discoveries that are valid, relevant, and largely ignored or misapplied in practice. ■

Jerry Avorn serves pro bono as an unpaid consultant to the Independent Drug Information Service (iDiS), which provides academic detailing to state governments. Michael Fischer serves as a paid consultant to iDiS.

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ABOUT THE AUTHORS: JERRY AVORN & MICHAEL FISCHER

Jerry Avorn is chief of pharmaco-epidemiology and pharmaco-economics at Brigham and Women's Hospital.

Jerry Avorn and Michael Fischer, colleagues at Harvard, are coauthors of a paper in this issue of *Health Affairs* on the necessity of identifying and overcoming barriers to implementing the results that are discovered in comparative effectiveness research.

Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmaco-epidemiology and Pharmaco-economics at Brigham and Women's Hospital in Boston. An internist, geriatrician, and drug researcher, he studies and writes about the risks and benefits associated with prescription medications and what influences prescribing decisions and patients' medication adherence.

Avorn directs the Harvard Interfaculty Initiative on Medications and Society. He championed the concept of "academic detailing" to provide evidence-based information about drugs to prescribing care providers. The author of more than 200 papers in the medical literature on medication use and its outcomes, Avorn received his medical degree at Harvard and completed his residency in internal medicine at Beth Israel Hospital in Boston.

Michael Fischer is a health services researcher and physician at Brigham and Women's Hospital.

Michael Fischer, an internist and clinical epidemiologist, is an assistant professor of medicine at Harvard and an associate physician in the Division of Pharmaco-epidemiology and Pharmaco-economics. He studies the impact of electronic prescribing; prescription drug reimbursement policy; medication adherence; the appropriate use of prescription drugs; and the assessment of complications of prescription drug therapy, especially among the elderly. He has also studied how scientific evidence and drug policy changes affect treatment patterns, the financial impact of physician prescribing habits, and the potential economic effects of increased use of generic medications.

Fischer earned his medical degree from the Yale School of Medicine and a master of science degree in epidemiology from the Harvard School of Public Health. He completed residency training in primary care internal medicine at Brigham and Women's Hospital. He now teaches in both the outpatient and inpatient components of the residency program and has an active primary care practice at Brigham and Women's Hospital.