

COMPARATIVE EFFECTIVENESS RESEARCH: A JOURNEY, NOT A DESTINATION

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Examples of past comparative effectiveness research illustrate both its promise and its limitations — and its impact on treatment patterns.

INTRODUCTION

The commitment of a \$1.1 billion “down payment” to support comparative effectiveness research by the American Recovery and Reinvestment Act of 2009 sparked a spirited discussion among those who see it as government interference leading to medical rationing and those who view it as the best way to curb the cost and improve the quality of healthcare.

It's not that simple.

Comparative effectiveness research is not a solution one buys like a red pill or a blue pill. It is a means, not an end. Two examples of past comparative effectiveness research illustrate both its promise and its limitations — and its impact on treatment patterns.

CLINICAL ANTIPSYCHOTIC TRIALS OF INTERVENTION EFFECTIVENESS (CATIE)

The first example involves the National Institute of Mental Health's multisite, pragmatic randomized clinical trial called Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). CATIE compared the effectiveness of several antipsychotic medications.

Antipsychotic medications are the number-one selling drug class in the United States, totaling \$15 billion in sales in 2009.¹ For years, debate raged in the psychiatric literature about whether newer antipsychotics were more effective than the older antipsychotics, as the pharmaceutical industry claimed. CATIE was designed to answer that question. The trial revealed that an older, moderate-strength antipsychotic was as effective as the newer antipsychotics.

What effect did these widely publicized findings have on sales of the older antipsychotic medications?

According to an analysis of Thomson Reuters healthcare claims data presented at the 2009 International Conference on Pharmacoepidemiology and Therapeutic Risk Management, the results of CATIE showed no significant increase in the use of older antipsychotics despite the finding of equal efficacy with the newer, more expensive medications.²

The most likely reason this large prestigious trial had no effect in actual clinical practice was that a primary concern with older antipsychotics was the risk of serious side effects. In particular, it was widely believed that older antipsychotics placed patients at higher risk for potentially permanent, disfiguring facial movement disorders called tardive dyskensia. The trial excluded patients at high risk for that severe adverse side effect. Thus, despite the evidence for equal effectiveness, providers were unconvinced that older antipsychotics were equally as safe as the newer medications. Patients and their providers were unwilling to trade off the equal effectiveness and lower cost for the risk of side effects.



THE ENHANCE TRIAL

On the other end of the spectrum, the second example is the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. This trial compared the cholesterol-lowering drug, simvastatin (Zocor), to Vytorin, which consists of simvastatin plus ezetimibe (Zetia), a drug that blocks cholesterol absorption from the gut.

Contrary to expectation, the pharmaceutical industry-sponsored ENHANCE trial found that the combination drug, Vytorin, did not reduce the amount of arterial plaque build-up in the carotid arteries, although it did lower low-density lipoprotein (LDL, the “bad” cholesterol) 56 percent compared to a 39 percent decrease in the simvastatin group, a statistically significant difference.³ The lack of reduction in arterial plaque build-up raised questions about Vytorin’s ultimate effectiveness and value relative to its cost.

Following these highly publicized results, sales of Vytorin and Zetia plummeted 22 percent in the United States from January, when the ENHANCE trial was published, through April 2008.⁴

COMMENTARY

What do these two examples tell us about the goal of developing more comparative effectiveness information and translating that information into everyday clinical practice?

First, they highlight that most medical interventions involve a complex balancing of risks and benefits. Risks and benefits typically vary from person to person and scientists, healthcare providers, and patients may weigh the harms versus benefits of medical interventions quite differently. In the case of the CATIE trial, scientists focused on the relative effectiveness of newer versus older, cheaper antipsychotics, but prescribers and patients were focused on the relative risks of the two medications.

Second, these examples illustrate that scientific information about the risks and benefits of interventions often emerge in unexpected ways. New results may be murky and contradictory. Prior to the ENHANCE trial, ezetimibe (Zetia) was widely used and perceived as an effective response to lowering cholesterol levels that failed to respond to initial treatment. After the trial was published, public opinion swung the other way. However, as the American Heart Association pointed out, the results muddied the waters more than anything and highlighted the need for more information.⁵ In particular, the ENHANCE trial was not large enough or long enough to determine whether the combination drug is more or less effective than the single drug in reducing heart attacks or deaths. Larger studies, like IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which is expected to be completed in 2012, are critical to assess cardiac outcomes and the potential of ezetimibe.⁶

It may also be argued that information on relative effectiveness should have preceded the wide adoption of medications such as ezetimibe. However, given the complexity of medical outcomes, one needs to be extremely careful of how the bar is set for adoption. For example, the lower risk of tardive dyskinesia with the newer antipsychotics was predicted based on knowledge about how the newer medications worked and secondary trial endpoints, but only experience with thousands of patients over time could reveal actual declines in the incidence of this relatively rare side effect.

Third, and importantly for the goal of incorporating comparative effective research into everyday clinical practice, a system that tries to constrain or offer incentives for particular medical protocols needs to be flexible and able to rapidly evolve to incorporate changes in medical knowledge. In some cases, unconstrained everyday practitioners may be the best front line for deciding how to respond to new information.

Developing an evidence-based medical care system that promotes the best and most cost-effective interventions is a goal that no one will argue with. However, we should recognize the continuing, often unpredictable flow of complex scientific information presents an ongoing challenge that will endure long after the last of the stimulus money is spent.

ABOUT THE AUTHOR

Tami L. Mark, PhD, is a nationally known expert on mental health and substance abuse services with extensive experience analyzing observational data. She is the director of analytic strategies at Thomson Reuters. In addition to publishing more than 70 peer-reviewed journal articles and numerous government reports, Dr. Mark has directed a number of large research projects for the pharmaceutical industry and federal government including retrospective analyses, prospective studies, chart review, and policy analysis. She has served on several government panels and journal editorial boards and is the coeditor of the Datapoints column of the journal, *Psychiatric Services*. Dr. Mark received her BA from Amherst College, her MBA from Loyola College, and her PhD in health economics from Johns Hopkins University.

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REFERENCES

1. IMS National Sales Perspectives. IMS Health. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20Therapy%20Classes%20by%20U.S.Sales.pdf. Accessed 3/21/2011.
2. Mark T. The impact of comparative effectiveness information on prescribing patterns: A case study. 25th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 16-19, 2009, Providence, RI.
3. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079524.htm>. Accessed 4/11/2011.
4. <http://www.fiercepharma.com/story/vytorin-zetia-scrips-drop-11-april/2008-05-29>. Accessed 4/11/2011.
5. <http://www.pslgroup.com/dg/21B22A.htm>. Accessed 4/11/2011.
6. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079524.htm>. Accessed 4/11/2011.

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