



ALLHAT and CATIE Reconsidered:
Reflections on Big Studies and Evidence Based Medicine as
the Measure of Comparative Effectiveness

CMPI
Center for Medicine
in the Public Interest

ALLHAT AND CATIE RECONSIDERED

**REFLECTIONS ON BIG STUDIES AND EVIDENCE BASED
MEDICINE AS THE MEASURE OF COMPARATIVE
EFFECTIVENESS**

Report of January 26, 2007

TABLE OF CONTENTS

Introduction.....	2
Panelists	3
Beginning of Discussion Panel	6
The CATIE Study.....	7
The ALLHAT Study.....	9
A More Individualized Alternative	11
Big Trials as a Basis for Reimbursement: Lessons from CATIE and ALLHAT	13
About the Center for Medicine in the Public Interest.....	17

INTRODUCTION

Recently Congress has considered adding cost-effectiveness as a criterion for selecting and paying for medicines under Medicare. This proposal, which is current practice in many nations, coincides with a growing effort among health insurers, health care foundations, and some policy analysts to have the government play a larger role in evaluating the comparative effectiveness of new medicines and devices in order to control the cost of health care. Indeed, the health care lobby, the Association of Health Insurance Plans has recommended that Medicare be given “explicit authority to use available data on comparative effectiveness and cost effectiveness deciding what drugs and services to cover and how much to pay.”

This model (variously called “evidence-based medicine,” “healthcare technology assessment,” or comparative effectiveness”) relies heavily on findings from randomized clinical trials. While these trials are essential to demonstrating the safety and efficacy of new medical products, the results are based on large population averages that rarely if ever will tell us which treatments are “best” for which patients. That is why it is so critically important for the physician to maintain his or her ability to combine study findings with their expertise and knowledge of the individual in order to make the optimal treatment decisions.

Government sponsored studies that conduct head to head comparisons of drugs in “real world” clinical settings are regarded as a valuable source of information for such coverage and reimbursement decisions, if not for making clinical decisions. Two such studies, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were two such “practice based” clinical trials sponsored in part by the National Institutes of Health to determine whether older medicines were as effective in achieving certain clinical outcomes as newer medications.

While media reports and the government agencies that sponsored the studies claimed that “older and cheaper” were equally effective, these conclusions were not without critics or controversy.

The Center for Medicine in the Public Interest held a conference on the effect of the Media on access and the application of Medicine and in Washington, DC on January 26, 2007 that included a panel on the coverage, conduct and implications of CATIE and ALLHAT for coverage decisions. At a time when evidence is becoming more genetic and personalized, the emphasis on large-scale trials is worth examining. This transcript raises these and other important questions that companies, patients and payors should consider in determining what data should be used to determine what medicines are best for patients.

Peter J. Pitts, President
Robert Goldberg, Vice President
Center for Medicine in the Public Interest
211 East 43rd Street 9th Floor
New York, New York 10017
(646) 414-0006 tel
(212) 588-8924 fax
info@cmpi.org

PANELISTS

Matthew Herper

Matt Herper is a staff writer for *Forbes Magazine* and Forbes.com. covering the biotechnology and pharmaceutical industries.

Susan Horn, Ph.D.

Susan D. Horn, Ph.D. is senior scientist for the Institute for Clinical Outcomes Research (ICOR), and vice president of research for International Severity Information Systems, Inc. (ISIS), both located in Salt Lake City, Utah. In addition, she is Adjunct Professor in the Department of Medical Informatics at the University of Utah School of Medicine in Salt Lake City.

From 1968 to 1991, Dr. Horn was a full-time faculty member at The Johns Hopkins University in Baltimore, Maryland, where she conducted research, taught biostatistics and health services courses, and directed the Robert Wood Johnson Foundation Program for Faculty Fellowships in Health Care Finance. From 1991 to 1995, she was senior scientist at Intermountain Health Care in Salt Lake City.

Herbert Meltzer, M.D.

Dr. Meltzer is Bixler/May/Johnson Professor of Psychiatry and Pharmacology and Director of the Psychobiology Program for Translational Research at the Vanderbilt University School of Medicine, Chairman of the International Psychopharmacology Algorithm Project, Chair of the Young Investigator Grant Review for NARSAD, and Director of the Schizophrenia Program of Centerstone Mental Health System.

A leading researcher in the pharmacologic treatment of schizophrenia, Dr. Meltzer played an integral role in the discovery of clozapine, the first atypical antipsychotic to be approved by the US Food and Drug Administration. He is one of the original members of NARSAD: The Mental Health Research Association's Scientific Council and chairs the organization's Young Investigator Review Committee. His research interests include suicide prevention and cognitive impairment in schizophrenia.

Kate Rawson

Kate Rawson is a senior editor of Windhover Information's *The RPM Report*, located in Washington, DC. *The RPM Report* provides in-depth analysis and intelligence on the regulatory and policy issues that impact business decisions.

Prior to joining Windhover, Rawson was an editor and reporter at "The Pink Sheet," where she covered FDA and CMS regulatory activities and business news. During her 10-year tenure at FDC Reports, she helped launch "The Pink Sheet" DAILY, an online daily publication on the pharmaceutical industry. Rawson also served as managing editor of "The Rose Sheet," which covers regulatory and business news of the cosmetics industry.

David Shern, Ph.D.

David L. Shern, Ph.D. is the president and CEO of the National Mental Health Association, the country's oldest and largest nonprofit organization addressing all aspects of mental health and mental illness. With more than 30 years of distinguished service in mental health services research and system reform, Dr. Shern is one of the nation's leading mental health experts. During his career, he has helped reengineer mental health care systems in Colorado, New York and Florida as well as participated in several national reform and research demonstration efforts.

Prior to joining NMHA in 2006, Dr. Shern served as dean of the Louis de la Parte Florida Mental Health Institute (FMHI) at the University of South Florida. With an annual budget of nearly \$45 million, FMHI's 500 faculty and staff work closely with all parts of the human services system to better identify, treat and prevent behavioral health problems. Home to five national research and training centers, FMHI conducts hundreds of community based studies each year in close collaboration with consumers, family members, providers and government partners throughout the United States.

Ralph Snyderman, M.D.

Dr. Ralph Snyderman is Chancellor Emeritus for Health Affairs at Duke University and President and CEO Emeritus of Duke University Health System and James B. Duke Professor of Medicine. He oversaw the development of the Duke University Health System, one of the few fully integrated academic health systems in the country. This integrated health system now provides an increasing continuum of care throughout North Carolina and beyond.

Dr. Snyderman accepted his first faculty appointment at Duke University Medical Center in 1972 as a Howard Hughes Medical Investigator, assistant professor of medicine and immunology, and Chief of Rheumatology at the Durham Veteran's Administration Hospital. By 1984, Dr. Snyderman became the Frederic M. Hanes Professor of Medicine and Immunology.

In 1987, Dr. Snyderman left Duke to join Genentech, Inc., a biomedical technology firm in San Francisco. While at Genentech, he led the development and licensing of several novel therapeutics and supervised 300 staff members working in pharmacology, clinical research and regulatory affairs.

Dr. Snyderman has received numerous honors and awards, including an honorary Doctor of Science degree from Downstate Medical Center of the State University of New York and a lifetime achievement award from the Arthritis Foundation. He has been recognized as a distinguished alumnus of both Washington College and the Downstate Medical Center of the State University of New York.

He is past Chairman of the Association of American Medical Colleges' Council of Deans and is the past Chair of the AAMC. He also is a member of the National Academy of Sciences' Institute of Medicine. Dr. Snyderman stepped down as chancellor for health affairs and president and CEO on June 30, 2004.

Michael Weber, M.D.

Dr. Weber is Professor of Medicine at the SUNY Downstate Medical College of Medicine, Brooklyn, New York.

Dr. Weber's career has been focused primarily on hypertension and preventive cardiology. He was one of the founders of the American Society of Hypertension (ASH) and has served as its President. He is currently Chair of the ASH Hypertension Specialists Program. A Fellow of the American College of Physicians, American College of Cardiology, and American Heart Association, Dr. Weber has served on the Cardiovascular and Renal Drugs Advisory Board of the Food and Drug Administration and continues as a consultant to that Agency. His current research interests are centered on clinical trials of patients with hypertension and those at high risk of cardiovascular events or recurrent strokes. He is also an active participant in trials involving patients with diabetic and nondiabetic nephropathy. Dr. Weber currently serves on the steering committees of several national and international clinical outcomes trials.

ALLHAT AND CATIE RECONSIDERED

KATE RAWSON: I am a senior editor of Windhover Information's *The RPM Report*. I'm going to kick off this panel by briefly discussing the media coverage for government-sponsored comparative effectiveness studies, and then the panel can debate the role of these studies as health care policy. We can debate whether government-sponsored comparative effectiveness studies are a growing trend, but the three most recent examples are ALLHAT, CATIE, and the Avastin/Lucentis study, which is being conducted by the National Eye Institute and The National Institutes of Health (NIH).

Avastin and Lucentis are both Genentech products: Lucentis is a relatively new drug for age-related macular degeneration (AMD). It's closely related to Avastin, which is approved to treat various cancers, but is widely used off-label for wet AMD. This will be an interesting study, and one I know we'll be following closely when the results are released in a few years. Although NIH says that it's not conducting the study for cost reasons, Avastin costs \$50 a dose, versus \$2,000 for a Lucentis dose, so there is a cost issue that the media will be keeping a careful eye on.

I'm going to use CATIE as a case study. Very briefly, 1,500 patients received either one of the four newer atypical antipsychotics or perphenazine, which is an older antipsychotic. When the first phase of the study was reported out in September 2005, the media grabbed onto the following statement from the NIMH press release: "Surprisingly, the older less expensive medication in the study generally performed as well as the newer medication."

The resulting headlines were somewhat conflicting. For example, the headline in the *The New Jersey Star Ledger*, the hometown newspaper for a number of large pharmaceutical companies in Northern New Jersey was: "Study Drug Built in the 1950's on Par With New Meds." *The Indianapolis Star*, which is home to Zyprexa manufacturer, Lilly, ran a markedly different headline: "Zyprexa Outperforms Rivals in U.S. Study."

So who was right? Well, you could make the case that they were both correct. Perphenazine was equally effective as the newer drugs and was as well tolerated. But Zyprexa was significantly more effective than all the other treatments by the primary outcome measure, which was time to discontinuation for any reason. That, of course, had to be weighed against the finding that Zyprexa patients also gained significantly more weight.

Part of the reason for the discrepancy in the media headlines could be due to the fact that CATIE was a very complex study. But the pharmaceutical industry was really well prepared for this. Drug companies had learned their lesson from the ALLHAT study in how to respond to these large government funded studies. And that was certainly reflected in the media coverage.

So where do we go from here? Are we going to see more government-sponsored studies like this in the future? They're certainly expensive – the question is, are they affordable? CATIE cost \$64 million, and ALLHAT cost \$128 million. That might not be much for a large pharmaceutical company, but it's certainly a pretty penny for the federal government.

One of the issues that we can debate today is whether or not that's money well spent. It was suggested on an earlier panel that perhaps money would be better spent on drug safety studies versus comparative efficacy trials, and that's something that the panel can certainly explore further. But one could question that given the waning fiscal generosity Congress has given NIH in recent years, these types of large-scale studies can't continue.

MATT HERPER: I cover health, medicine, and science for *Forbes* and Forbes.com. The reason these government-run stories have been such a big story -- and the thing that will perk an editor's ears when you mention one -- is that there's an impression that the government's done the perfect clean study and it shows all these drugs are the same and all this marketing has been simply hype. I've noticed that every time there's a government study, it always seems to show no difference between the treatments.

That's why these are so interesting. In an environment where the government is increasingly paying for health care, it does seem we need more information about these drugs. And in fairness, there often aren't a lot of comparative studies that have been done by the industry.

The media is in a bit of a confusing situation because we are looking at a whole bunch of expensive studies paid for by taxpayer dollars, and we're looking at it trying to find a lesson. Having these studies as a counterpoint to what has come out of industry is very important and something that we as storytellers are very interested in.

THE CATIE STUDY

HERBERT MELTZER: I'm a professor of psychiatry and pharmacology at Vanderbilt. I have been a consultant to all the pharmaceutical companies and often a grantee that have been involved in CATIE. But the majority of my research support has always come from the NIMH. I helped design CATIE up to a certain point and then dropped out of the process as certain things got uncomfortable in terms of the way things were going. But I remain actively involved in the CATIE publication process. I'm very positive.

Kate mentioned the possibility that one or both of those newspaper stories were correct. There's actually another possibility: that neither were correct. I'll try to show you where that might be the case. This is supposed to be a "pragmatic" trial. But as you get into the design, which was very complex, it really was not an effectiveness study. It had much too much of the paraphernalia of a randomized controlled trial that really made it very different from what it was supposed to be -- a look into the real world of patient population and how doctors treat patients. In contrast to the sterility, if you will, artificiality of a regulatory trial.

The media were really only reflecting what NIMH said about the study -- that there was little difference, if any, between the older atypical antipsychotic, perphenazine, and the newer drugs either in efficacy or safety. The fact that the costs were enormously different between these products gave a strong implication that the only reason they dominate the clinical arena was drug company hype and detailing, and that there was really no substance to the claims.

When CATIE came out, much to everyone's surprise, the results were really quite inconsistent with evidence-based medicine. One comment on the media was why there such a readiness to accept this as the definitive word -- accept the view of the NIMH that this was the best, largest, longest, most definitive answer to a very

complex question, when it really stood and still stands in opposition to just a huge body of evidence-based medicine?

So that puts the media in a very difficult position. I gave a talk right after this came out, and some patients accused us psychiatrists of lying to them all these years. Those were the words: “You said these are much better, safer drugs and they’re really not. We don’t believe you.” But interestingly, CATIE has had, to my knowledge, very little impact on the field. And we can discuss why that is, but basically it’s because the findings were not consistent with clinical practice.

So why was there such a discrepancy between the study results and evidence-based medicine? First, there were a number of problems with the design. That happened because of the many stakeholders who contributed to it; because there was an over-ambitiousness in this big “expensive” trial – the very first one NIMH ever did – to answer too many questions. But while the study was complex, it didn’t begin to address the complexity of schizophrenia. And yet people took away from it a bottom line that what they found in that study applied to all of this extremely heterogeneous disease.

The main flaw had to do with the kind of patient population that went into that trial. When you look at how well olanzapine did in the CATIE study, it was due to the inclusion of treatment-resistant patients and allowing that one drug to be used at three times the dose that is needed to treat the average schizophrenic.

But the most intriguing part of this thing and one of the biggest reasons I didn’t want to get that close to it, was the choice of primary endpoint: all-cause time to discontinuation. Whatever reason the patient or physician chose – lack of efficacy, intolerability or something very vague called “patient choice” – it was used as the primary measure. And between 60%-80% of patients switched therapy.

The whole point of the study was to encourage patients to switch from one drug to another – there was no incentive for patients to stay on their initial drug. That accounted, in part, for why these drugs didn’t do so well. The major focus right now of our research is to improve cognition in schizophrenia, not to treat the positive symptoms. And that was not at all addressed in the first round of this study.

**“THE MAJOR FOCUS RIGHT NOW OF OUR RESEARCH IS TO IMPROVE COGNITION IN SCHIZOPHRENIA, NOT TO TREAT THE POSITIVE SYMPTOMS. AND THAT WAS NOT AT ALL ADDRESSED IN THE FIRST ROUND OF THIS STUDY.”
HERBERT MELTZER M.D.**

The second phase of the study was so poorly designed that it’s hardly worth even describing. But I’ll just tell you the major flaw: they compared clozapine, the supposed gold standard in this class of drugs, with the other atypicals. And they again used all-cause time for discontinuation as the primary endpoint. The patients who got into that trial wanted to take clozapine. Clozapine was given on an open basis, whereas all the all other drugs were blinded. So as soon as they got into the blinded phase, most of those people switched until they got on clozapine. And that was considered a win for clozapine.

So there are many good things about the CATIE study that we’ll learn from it. There’s going to be probably some very excellent pharmacogenomics. What I hope to see the media do is to revisit this story, really looking into it in depth and trying to see what holds up over time.

But from the point of view of the message to the public and to the payers -- that these

drugs are equal and that the pharmaceutical industry has been pulling the wool over the eyes of everybody about this, I think that there was a disservice.

DAVID SHERN: I'm the President of Mental Health America, which was previously known as the National Mental Health Association. CATIE is a particularly good case study – oftentimes you would kill to get that kind of press on one of your studies. It's a good case study for the role of an advocacy public education organization, and perhaps to do a little bit of 20/20 hindsight on how we might have tried to move some of the more subtle messages that Dr. Meltzer discussed.

When Clozaril showed up as the first of the second-generation agents, it was initially greeted as a miracle drug. People were talking about awakening individuals who'd previously been non-responsive. So there was a tremendous public expectancy for the next generation of atypical antipsychotics. There was this tremendous receptivity on the part of consumers, family members and practitioners for these new miracle drugs.

At the same time, we're in a very strong cost-containment environment and we're desperate for ways to increase the effectiveness and efficiency of our system. Given the cost-containment environment and overall cynicism about the pharmaceutical industry, the media was quick to pick up on the finding that there was no meaningful difference in symptom reduction between perphenazine and the next-generation products.

“WE ALMOST IMMEDIATELY FOUND OURSELVES IN KIND OF A REACTIVE MODE TRYING TO BLUNT AN OVER-SIMPLISTIC INTERPRETATION OF THE RESULTS OF THIS VERY BIG AND COMPLICATED STUDY.”

**DAVID SHERN,
MENTAL HEALTH AMERICA**

And from our perspective, probably one of the biggest messages to come from this study was the fact that there was an awful lot of discontinuation in general. If you're getting that kind of switching, it probably says that we haven't quite gotten where we need to get in terms of having this next generation drug.

In hindsight, if you look just at symptom measures, there was no main difference, but the story is much more complicated than that. From our perspective, the bigger story was the fact that there was a tremendous amount of switching, that probably tells us a little bit about the idiographic nature of the response and the importance that clinicians and patients get to have a full range of alternatives with which to work. Within a public health perspective, cheaper is always better if everything else is equal.

Our challenge working with the media is how to tell an interesting story – so it's not just a rewrite of medical journals. Somehow what we need to do is get better and faster at positioning these stories and telling them in a more compelling way than I think we did here.

THE ALLHAT STUDY

MICHAEL WEBER: I'm a cardiology person. I'm at the State University of New York, the Downstate Medical College. I'm involved with a number of very large-scale clinical trials. I want to make some comments about ALLHAT, because ALLHAT was a watershed study that casts light on a government agency, its value and its ethics.

The origin of ALLHAT was from the very beginning to be a political and economic clinical trial. The hope for the study was to show that an older, cheaper drug, a generic diuretic would be at least as good as newer expensive drugs – Norvasc, a calcium-channel blocker and Prinivil, an ACE-inhibitor.

The study went on for several years. It turned out to be a little disappointing due to flaws in the design, and perhaps some misadventure as well. The endpoint of the study was heart attacks. To the agency's disappointment, there was no difference whatsoever between the treatments in heart attack incidents, even though blood pressure favored the diuretic.

Meanwhile, the head of the National Heart, Lung and Blood Institute (NHLBI), now departed from the job, had already promised Congress that they would show the beneficial effects of the diuretic. What then was he to do with these discouraging results? Well, he did what anyone else would do – they hired Ogilvy, the PR firm. Let me read you the three-bullet headline from *The Wall Street Journal*: (1) “Study Questions High-Cost Drugs for Hypertension”; (2) “Big U.S. Effort Finds Diuretics Can Be More Effective Than Industry Blockbusters”; (3) “Unusual Boost for Generics.”

The New York Times had similar headlines, but also ran a charming auxiliary article entitled, “Diuretics Value Drowned Out by Trumpeting of Newer Drugs.” Where did all this come from? It came from very creative press work by the people that were hired by the NHLBI. To its credit, three days later, *The New York Times* – presumably by then they actually had read the article – published a correction on page two of their paper

The reality of ALLHAT – it was poorly designed, the interpretations were disingenuous, it violated appropriate scientific reporting, and most frightening, it did something that was so unethical that if a pharmaceutical company had done it or any of us as individual academics had done it, we would not only be thrown out of our jobs, we would be pilloried and maybe even be facing criminal charges: And one thing that did show up in favor of diuretics, the fact that they cause fewer strokes than one of the other drug classes, was driven entirely by a 40% excess stroke rate in black patients that was predictable before the study began. And they used that as their reason to claim superiority of the diuretic.

Can you imagine if Merck had done that, or Bristol-Myers Squibb, or Novartis? There'd be no end to the human cry. And what's very disturbing is that every time I've raised this ethical issue, no one has refuted it. It tells us a couple of things. First of all, NHLBI is not sacred, it's not in any way an agency that has any special high level of morality. It's just another government agency that has the same questions about its integrity as anyone else who survives by pandering to the perceived needs of its political masters. And anyone who says clinical trials are so important we have to hand them off to government agents, because we can't trust industry – that's absolute nonsense. It should be the other way around. If something's important, for God's sake don't give to a government agency. Ask some reputable people on the outside who'll bring some integrity and honesty to it.

**“ALLHAT EXPOSED
AFRICAN-AMERICAN
PATIENTS FOR SEVERAL
YEARS TO TREATMENTS
THEY KNEW WOULD NOT
BE EFFECTIVE IN
CONTROLLING THEIR
BLOOD PRESSURE.”
MICHAEL WEBER, M.D.**

The other thing that's upsetting is the fact that people still talk about ALLHAT as a sort of the grand paradigm of evidence-based medicine. This is not evidence-based medicine – this is information that when you look at it, analyze it, think about it, it's fascinating and you can learn lessons from it. But evidence is what you make of it. You can draw all sorts of conclusions from the same evidence.

A MORE INDIVIDUALIZED ALTERNATIVE

SUSAN HORN: I'm from the Institute of Clinical Outcomes Research. We are finding that there are other ways to be able to answer questions than just what they've called evidence-based medicine based on randomized control trials. I'm going to very quickly describe that to you only for the purpose of getting to several examples where we have found actually contrary to findings in various randomized trials, that we can only by looking at the actual practice of care, be able to even discover what might be best for particular subsets of patients.

The kind of study designs that we have been doing have been called practice-based evidence studies, where rather than using enrollment criteria, as happens in randomized trials, everybody with a condition is considered part of one of these studies. In randomized trials, there are always a large number of exclusionary criteria because you want to be sure that you're looking at a rather homogenous population of patients. In the practice-based evidence studies, nobody is excluded.

**“THE MORE MANAGED CARE LIMITED ACCESS TO MEDICATIONS, THE MORE HOSPITALIZATIONS AND VISITS TO PHYSICIAN OFFICES AND EMERGENCY ROOMS.”
DR. SUSAN HORN**

On the treatment side, randomized trials are powered to one specific outcome. In practice-based evidence studies, there are a lot of things that we really don't know how they're interacting with each other in multiple combinations. So we measure everything that's going on in the process of care, including medications, nutrition, exercise, etc.

One of the first studies we did with this new methodology was the Managed Care Outcomes Project, where we wanted to look at limiting access to care that managed care organizations were doing back in the early to mid-'90s. We looked at very common ambulatory diseases, and we followed over 13,000 patients over a one-year period.

The biggest surprise in this study was the fact that no matter how we discounted the cost of the medications, the overall costs were higher, and so were the number of prescriptions. The more managed care limited access to medications, the more hospitalizations and visits to physician offices and emergency rooms. So we found that limiting access was not going to be the way we were going to be able to get better outcomes.

Another thing we looked at was limiting access to mental health services. In this medically ill population, there were a large number of people who had depression or were on antidepressants. But very few people had access to mental health providers. That's usually one of the limitations that you find in most managed care plans. They won't allow access to mental health providers.

Those people who were not getting the best medications or seeing mental health providers were using about 50 percent more non-psychiatric medications. In other words, they weren't feeling well, so they kept getting more and more other drugs. They were having about 50 percent more non-psychiatric visits. They had more non-psychiatric hospitalizations. In other words, we think we're saving money by this practice of limiting access, but we were actually spending much more for these people because we were not addressing their underlying illness.

We also did a long-term care study looking at 2,500 long-term care residents. We came up with a huge surprise with regard to psychiatric medication. One of the great fears in long-term care is for the facilities to use chemical restraints on people in

nursing homes. So there's a national guideline that advises to use the fewest number of medications possible. Then they recommend using newer antipsychotics and antidepressants instead of benzodiazepines, and avoid combination therapy.

We actually were trying to show that the guideline was right, but we actually showed just the opposite: Combination therapy of a new SSRI and a new antipsychotic resulted in these frail, elderly, demented patients having the fewest hospitalization and emergency room visits, the least amount of restraint use, and the lowest number of pressure ulcers.

We've also found interesting things about the use of psychiatric medications in people who've had a stroke. If someone's had a stroke, you usually don't use any psychiatric medications because you don't want to compound it with a drug that could affect the brain. And yet we found that the people that were on new atypical antipsychotic had a much better recovery.

So we can't just rely on randomized trials to learn about what is best for specific types of patients. If we look in the actual practice of care, there's a great deal we can learn. People are always talking about evidence-based medicine. I think we need to talk more about practice-based evidence.

RALPH SNYDERMAN: I'm Ralph Snyderman. I was a physician-scientist working on research and inflammation for a number of years in rheumatology, spent some time at Genentech as senior VP for medical research and development at the time Herceptin was put into development. And then I spent 15 years at Duke in charge of the medical center and health system.

I'm interested in personalized, predictive and prospective approaches to health care – in overseeing the Duke health system, it struck me how distorted the practice itself actually is. I'm a rheumatologist. And for many, many years we had first one and then dozens of non-steroidal anti-inflammatory agents that we would walk patients through from A to Z. Now we have the biologics, Enbrel, Remicade, Humira. Some respond to some, some to others, some not at all, some get tuberculosis. And yet, that's the way we're practicing medicine.

Any rheumatologist could tell you that rheumatoid arthritis is not one disease; there are probably at least three and maybe six, and there may be more. Given that, I am interested in how we can get physicians to start practicing in a more informed way in regards to their specific patients' own needs. I've called it prospective health care, personalized, predictive, preventative medicine.

I'll give you two examples. One is cancer chemotherapy. Cancer chemotherapy obviously is extremely important in the treatment of cancer but it's heavily distorted in terms of how it's practiced because of severe unanticipated outcomes, primarily bone marrow suppression. Depending on the tumor – let's say breast cancer – 11 percent of individuals given full chemotherapy for breast cancer will get febrile or severe neutropenia. The problem is the physician doesn't know which one. There are certain biases on the part of the medical oncology that to avoid febrile and severe neutropenia you decrease the dose of chemotherapy, increase the length, and what medical oncologist say, "kill with kindness."

So how do we get around it? I formed a little company to develop risk-assessment tools that could enable physicians to make better decisions. In collaboration with my academic colleagues, we conducted a 5,000-patient prospective trial of patients

undergoing cancer chemotherapy. You can follow individuals over time and look at virtually anything – clinical parameters, lab test parameters, etc. And then you analyze the risk predictive factors that give you a likelihood for incidence of febrile or severe neutropenia. This could be put together in an algorithm for physicians in ways that they can actually use it. They get their patient-specific risk profiles compared to this large database. They could then specifically try to customize the therapy with the patient with the tumor to minimize the risk of cancer chemotherapy.

“HOW DO WE START PREPARING THE MIND OF THE PHYSICIAN, THE PROVIDER AND THE PATIENT TO UNDERSTAND THE IDEA THAT RISK AND BENEFIT IS HIGHLY PERSONAL?”

We are moving into an area in which molecular medicine – let’s say, systems biology – allows us to try to anticipate events. For the first time in medicine, we are evolving the capability to predict risk. My goal has been to say, how do we get this into practice?

KATE RAWSON: Matt, I wonder if you can talk a little bit about the role of the news media is in communicating the results of these large government sponsored outcome studies.

MATT HERPER: We’re probably more likely to write a story on an NIH trial, than whatever the latest industry-sponsored study, because there are so few of these government sponsored trials and we are looking for a counterpoint to the large volume of studies produced by the pharmaceutical industry.

As a reporter, clinical trials are great to cover because sometimes they actually have real clear answers, which is hard to come by in a field like science and medicine. Actual facts can be a very nice thing to have to build a story around. They’re wonderful.

KATE RAWSON: For the rest of the panel, I’d like to reflect on the future of these large scale trials, and whether they mean really anything as we start to evolve towards personalized medicine. Do these large scale trials have a place in the scientific community? Or are they really the only thing that we can trust right now?

BIG TRIALS AS A BASIS FOR REIMBURSEMENT: LESSONS FROM CATIE AND ALLHAT

HERBERT MELTZER: As the examples of CATIE and ALLHAT show, the government has its own biases that we all have to be really concerned about. In defense of NIMH, the CATIE study was the first time they did a study of that size, and they were pulled into it – it came from on high that the NIMH should be spending money this way. I hope they can learn from their mistakes.

“NO MATTER WHERE IT COMES FROM, IF THE STORY LOOKS TOO GOOD TO BE TRUE IT PROBABLY IS. I COULD HAVE READ THE EXACT SAME HEADLINES IN *THE WALL STREET JOURNAL*, IN *THE NEW YORK TIMES*, IN *THE WASHINGTON POST* THAT YOU DID FOR ALLHAT.”

HERBERT MELTZER, M.D.

No matter where it comes from, if the story looks too good to be true it probably is. I could have read the exact same headlines in *The Wall Street Journal*, in *The New York Times*, in *The Washington Post* that you did for ALLHAT. If I had to give advice to the media, I would encourage them to get behind the story as much as possible. Why is this coming up? What does it really mean?

MICHAEL WEBER: These are all very complicated things, and the hard thing is how to come up with a story that's easily communicated. We learn things from observational studies for sure, but when we get back to clinical trials it's a very different scenario, because it's a very, very small difference that you're looking for in a very controlled, non-representative sample. Somehow we need to balance all of this stuff.

JOHN FLYNN: I was in Oregon a couple weeks ago and I met with a group of folks that run the Drug Effectiveness Review Project (DERP)¹. It was terrifying to me to learn that DERP weighs in across 20 different classes. And without exception in every analysis they did they ended up saying, there is no important difference between the cheapest drug in the class and any other drug in the class. That to me is remarkable. It's unusual when you analyze any data set and come up with any kind of uniform result like that.

DERP is considered the gold standard by at least 18 state Medicaid agencies. It is a freight train. You're presenting such a fundamental disconnect between reality and what is driving reimbursement decisions for new drugs coming out of the pipeline. Isn't there a story here from the press perspective? I know people are cynical about big, wealthy, international firms, but aren't they cynical of government too? Where's the story and how do you get through this divide?

HERB MELTZER: I predict that with the atypical antipsychotics, if DERP or anybody really tried to limit access in a significant way, the pushback from the field would be so enormous that we'd never get away with it. It just can't happen because the reality is that in clinical practice with the majority of patients there is a very big noticeable difference.

PETER PITTS: It seems to me that the cost effective study from CATIE is the big winner from a generic perspective. Is there an opening for payers to start requiring patients to first try the generics before Risperdal, for example?

HERB MELTZER: It's a difficult question to answer specifically. There are enormous problems. When you look at the confidence intervals, the study did not have the power to definitively say that any one of the drugs was really more cost effective than another. And the paper got published despite enormous commentary from the reviewers that this paper shouldn't be published. But it was government-sponsored, there was so much interest, it nevertheless got out in the field.

I would say, yes, there are differences in cost effectiveness between these drugs that should drive clinical decision making down the road, but let's be careful where we get the data and how we get the data to answer that cost effectiveness question.

The problem with CATIE was that they wanted to put in everything and the kitchen sink. Instead of just focusing on an effectiveness model, it came to be all things to all people. And that became its undoing.

If they had gone back to the return on investment model to some extent, they might've had a much better chance. We might see the government actually doing something that's in that scale and scope that could be useful.

PETER PITTS: Regarding the DERP model and the ability for large payers to deny payment for certain large classes of drugs, the comment that the patient population would never let it happen is positive. I'd like to think that was true.

But I think if you look at what's happening from large payers, the reverse has happened. Governments and private payers are making decisions. And if patients don't like it they can go someplace else, if there is someplace else to go. If we can't rely on patient groups to make payers do the right thing, what are you working on to help payers do the right thing?

SUSAN HORN: For the payers who doubt whether certain treatments are associated with better outcomes for specific types of patients – by having those comprehensive databases, we usually have the data to address their doubts. So they'll say, "well, this might've worked in this case, but I'm worried about patients of some other descriptors." And with the databases, we can pull out large samples with just those descriptors and be able to show what happens.

As you heard from my colleagues, it's very difficult to do randomized trials with combination therapies. To my knowledge, there isn't even a study design that the FDA has to be able to look at two drugs at a time. They really can only look at one drug at a time in various practices for various settings. But you can look at many combinations that might be much more logical in the actual practice and pair it with practice-based evidence studies.

I had no idea what CATIE and ALLHAT cost. None of the studies that I've shared with you cost more than \$1 million. So we've got orders of magnitude differences in terms of what the costs are to do practice-based evidence studies.

RALPH SNYDERMAN: If you do have a predictive methodology that determines populations that will benefit from one thing versus another, how do you start using it? How do you get insurers to reimburse rationally through the use of a therapeutic that could be very expensive but beneficial, as opposed to not reimbursing? And how do you get physicians to start using it that way?

"WE ALREADY HAVE A VERY GOOD VALIDATED MODEL TO BE ABLE TO PREDICT WHO BENEFITS AND WHO DOESN'T FROM DIFFERENT MEDICINES.

AS WE GET BETTER WAYS OF PREDICTING, HOW DO WE PUT IT INTO PRACTICE, AND THEN HOW DO WE REMOVE THE OBSTACLES? THERE ARE TREMENDOUS OBSTACLES: REIMBURSEMENT IS ONE AND REGULATORY POLICY IS ANOTHER."

RALPH SNYDERMAN, M.D.

To some degree the FDA may play a role by requiring that a good predictive marker be used to prescribe the drug and insurers may become more enlightened to support these kinds of studies. We are engaging in a pilot with Blue Cross/Blue Shield North Carolina to try to develop the methodology to rationalize the use of very expensive biological therapeutics, such as GCSF. We already have a very

good validated model to be able to predict who benefits and who doesn't from

different medicines.

As we get better ways of predicting, how do we put it into practice, and then how do we remove the obstacles? There are tremendous obstacles: reimbursement is one and regulatory policy is another.

DAVID SHERN: Our jobs in terms of health charities is really translating the science as best we can to the media, also to primary consumers and their family members so they can make the best decisions possible given the state of the science. And we need to be good critical leaders and translators. And then, secondly and perhaps more importantly, we need to put the patient's face on the condition and really bring a voice to that in a powerful way.

We're a member of the National Health Council and we decided to start to talk specifically about issues of universal access and the opportunity over the next 18 months, given the Presidential election cycle, to finally push that over the top. Somehow, our job is to put the patient's face on this so that it's less abstract, but do it in as science informed way as we possibly can.

About the Center for Medicine in the Public Interest

The mission of the Center for Medicine in the Public Interest (CMPI) is to discuss, debate, and demonstrate how exponential and accelerating technological progress coupled with smart public policy will enhance and advance 21st century health care by predicting, preventing, diagnosing, treating and disease with greater speed, more precision, and less cost. It has established the Patient-Centric and Prospective Medicine Project to insure that the policy and regulatory roadmap for this revolution is put in place now as opposed to the creation of a one size fits all approach to reimbursement and product approval.

For more information please visit www.cmpi.org and our blog at www.drugwonks.com.

CMPI Co-founders

Peter J. Pitts,
Robert Goldberg, Ph.D.

President
Vice President

ppitts@cmpi.org
rgoldberg@cmpi.org
bobgoldberg@yahoo.com

ⁱ The Drug Effectiveness Research Project is part of the Oregon Evidence-based Practice Center at the Oregon Health and Science University. It was established in 1997 to provide legislator reviews of evidence from clinical research studies – mostly randomized clinical trials -- for use by policymakers in decisions on guidelines and coverage issues. DERP is a collaboration of public and private organizations, including fifteen states, that have joined together to provide systematic evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes and to apply the findings to inform public policy and related activities. Recently, after criticism that its recommendations were being used to drive patients to specific medicines, the Oregon Health and Science University added this disclaimer to the DERP website:

The purpose of the DERP reports is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes.

Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports. <http://www.ohsu.edu/drugeffectiveness/>