



**CMPI**

Center for Medicine  
in the Public Interest

The New Vital Force in Health Care Policy

**Personalized Medicine and Responsible  
Access to Pain Medication**

**Comments and commentary from the Capitol Hill conference held on  
September 10th, 2013  
in the Rayburn House Office Building**

**Personalized Medicine and Responsible Access to Pain Medication**

**A Capitol Hill Briefing**

***September 10, 2013 from 9:30AM – 2:15PM***

**AGENDA**

**10AM: Welcome**

Peter Pitts, Center for Medicine in the Public Interest

**10:15: Keynote: FDA Regulation and Responsible Access to Pain Medication**

Douglas Throckmorton, Deputy Director, Regulatory Programs, CDER, FDA

**11:00: Access to Pain Medications: The Role of Patients and Manufacturers**

Moderator: Steve Usdin, BioCentury

Cindy Steinberg, US Pain Foundation

Bob Twillman, American Academy of Pain Management

Stuart Kim, Mallinckrodt Pharmaceuticals

**12:00: Issue: Pain Medications: Two Reporters Views**

Moderator: Peter Pitts, CMPI

Steve Usdin, BioCentury

Judy Foreman, Syndicated Columnist

**1:30: Closing Keynote: Pain Medications and the Future of Personalized Medicine**

Introduction: Peter Pitts, CMPI

Charles Inturrisi, Weill Cornell Medical Center

**2:15: Closing Remarks**

Peter Pitts, Center for Medicine in the Public Interest

**Peter J. Pitts**

Peter Pitts is President and co-founder of the Center for Medicine in the Public Interest. Prior to founding CMPI, Pitts was a Senior Fellow for healthcare studies at the Pacific Research Institute.

From 2002-2004 Peter was FDA's Associate Commissioner for External Relations, serving as senior communications and policy adviser to the Commissioner. He supervised

FDA's Office of Public Affairs, Office of the Ombudsman, Office of Special Health Issues, Office of Executive Secretariat, and Advisory Committee Oversight and Management. He served on the agency's obesity working group and counterfeit drug taskforce.

His book, *Become Strategic or Die*, is widely recognized as a cutting edge study of how leadership, in order to be successful over the long term, must be combined with strategic vision and ethical practice. He is the editor of the new book, *Coincidence or Crisis*, a discussion of global prescription medicine counterfeiting.

He has served as an adjunct professor at Indiana University's School of Public and Environmental Affairs and Butler University.

### **Douglas Throckmorton**

Dr. Douglas Throckmorton is the Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA). In this role, he shares responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter and generic drugs in the U.S. From aspirin to cancer-treatments, CDER works to ensure that the benefits of approved drug products outweigh their known risks.

Dr. Throckmorton has been at the FDA since 1997. He received his training in Internal Medicine and Nephrology from the University of Nebraska Medical School, Case Western Reserve University and Yale University. Prior to coming to the FDA he was a basic science researcher and academic physician at the Medical College of Georgia and the Veterans Administration Hospital in Augusta Georgia.

### **Steve Usdin**

Steve has been Washington Editor of *BioCentury* since 1993, and has spent the past 20 years in the nation's capital covering political and policy issues affecting the life sciences sector.

He also is the host of *BioCentury This Week*, *BioCentury's* weekly public affairs television program, as well as *BioCentury* Senior Editor responsible for coverage of

social issues involving biotechnology. Steve's reporting about biotechnology and biomedical policy has been cited in *The Economist*, *The Wall Street Journal*, the *Washington Post*, *New Scientist* and other publications.

In 2012, the FDA Alumni Association named Steve the Harvey W. Wiley Lecturer, making him the first journalist to receive the Wiley Award. His book, "Engineering Communism: How Two Americans Spied for Stalin and Founded the Soviet Silicon Valley," was published in 2005 by Yale University Press.

### **Cindy Steinberg**

Cindy Steinberg is the National Director of Policy and Advocacy for the U.S. Pain Foundation, a member of the Steering Council of the Massachusetts Pain Initiative (MassPI) and Chair of MassPI's Policy Council. Ms. Steinberg is New England Director of the American Chronic Pain Association (ACPA) and Leader of the Boston Area Chapter of the ACPA, which she founded in 2000. She is also a member of the Leadership Advisory Council for the State Pain Policy Advocacy Network (SPPAN), the Advisory Council for the Massachusetts Prescription Monitoring Program and the Joint Policy Workgroup on Opioid Prescribing established by the Massachusetts Legislature in 2012.

Ms. Steinberg is a passionate and articulate spokesperson for the needs of those living with pain. She has given numerous speeches and workshops on pain management and pain policy at national and local conferences and healthcare institutions and has been interviewed in print and on radio, television and internet websites. Ms. Steinberg testifies regularly at hearings at both the state and federal level on pain policy matters. In 2009, Ms. Steinberg was awarded the *American Pain Foundation's Presidential Medal* for outstanding contributions to the field of pain management. In 2010, Ms. Steinberg received the *State Pain Initiative Champion Award* from the Alliance of State Pain Initiatives for her pain policy accomplishments. In August of 2013, Ms. Steinberg was selected as one of six leaders in the field of pain management to receive the prestigious *Mayday Pain & Society Fellowship* for 2013-2014.

### **Bob Twillman**

Bob Twillman, Ph.D., is the Deputy Executive Director and the Director of Policy and Advocacy for the American Academy of Pain Management. In that capacity, Dr. Twillman is responsible for overseeing federal and state pain policy developments and advocating for those supporting an integrative approach to managing pain. He also serves as Chair of the Prescription Monitoring Program Advisory Committee for the Kansas Board of Pharmacy. Dr. Twillman received his Ph.D. in Clinical Psychology at

the University of California in Los Angeles, and maintains a volunteer faculty appointment as Clinical Associate Professor of Psychiatry and Behavioral Sciences at the University Of Kansas School Of Medicine in Kansas City, KS. Prior to taking his current position, Dr. Twillman was a full-time faculty member at the University of Kansas Medical Center, where he founded and directed the inpatient pain management program and was a co-founder of the hospital's Palliative Care Team. He has been actively involved in pain policy through his work with the Alliance of State Pain Initiatives and the American Pain Society for many years.

### **Stuart Kim**

Stuart Kim is Associate General Counsel, Regulatory Affairs of Mallinckrodt Pharmaceuticals (Hazelwood, MO). His legal/regulatory expertise includes good manufacturing practice ("GMP"), good clinical practice ("GCP"), pharmacovigilance and Risk Evaluation and Mitigation Strategies ("REMS"), and prescription drug life cycle management.

Previously, Mr. Kim has worked as in-house regulatory counsel for two pharmaceutical companies, was an associate with the law firm of McKenna Long & Aldridge LLP (Washington, DC), and served as a research analyst for the National Bioethics Advisory Commission ("NBAC").

Mr. Kim earned his J.D. from the University of Wisconsin Law School. In addition, he has an M.S. in Anatomy from the University of Wisconsin-Madison, an M.S. in Biological Sciences from the University of Notre Dame, and a B.S. in Biology from Lafayette College.

### **Judy Foreman**

Judy Foreman is a nationally syndicated health columnist whose "Health Sense" columns have appeared regularly in the Boston Globe, Los Angeles Times, Dallas Morning News and other national and international outlets. For years, she also wrote the Globe's popular short feature, "Health Answers."

She graduated Phi Beta Kappa from Wellesley College, served in the Peace Corps in Brazil for three years, then got a Master's degree from the Harvard Graduate School of Education. From 2001 to 2004, she was a Lecturer on Medicine at Harvard Medical School and, for most of this time, was a scholar at the Brandeis Women's Research Center. She has also been the host of a weekly, call-in radio show on Healthtalk.com and has won more than 50 journalism awards.

Her book on chronic pain, "A Nation in Pain – Healing Our Biggest Health Problem," is due out in January, 2014 from Oxford University Press.

### **Charles Inturrisi**

Dr. Charles Inturrisi is Professor of Pharmacology, Weill Cornell Medical College. He also has appointments in the Neuroscience Program at WCMC and with the Pain and Palliative Care Service, of the Memorial Sloan-Kettering Cancer Center and with the Drug Abuse Center at The Rockefeller University.

Dr. Inturrisi's current research is measuring the long term outcomes of treatments for chronic cancer and noncancer pain received by patients at four hospital-based outpatient Pain Clinics. He continues to have an interest the role of glutamate receptors in injury-induced pain and opioid tolerance, dependence and addictive behaviors. His research is directed at the discovery of new treatments for pain and drug addiction.

Dr. Inturrisi has received the John J. Bonica award of the Eastern Pain Association, a Distinguished Alumnus award from the University of Connecticut and the Excellence in Mentoring Award, Weill Cornell Medical College Postdoctoral Association. In 2008, Dr. Inturrisi received the first Graduate Dean's Award for Excellence in Teaching and Mentoring of Graduate Students, presented by the Weill Cornell Graduate School of Medical Sciences.

He served as the president of the American Pain Society from 2008 to 2010 and in 2013 received the Distinguished Service Award from APS.

He was a member of the Institute of Medicine Committee that prepared the 2011 Report entitled "Relieving Pain in America".

### **Pain, Patients, and Public Policy**

Peter Pitts: My name is Peter Pitts. I'm the President of the Center of Medicine in the Public Interest. I'm a former FDA Associate Commissioner. I would like to mention one thing before I begin my prepared remarks. The FDA does not get the credit it deserves for working not only very

hard but in an extraordinarily caring way on the issue of pain medications. It's important to understand that the folks at White Oak and, Doug Throckmorton particularly, understand things from the patient perspective. They understand the difficulties of doing the right thing from a law enforcement perspective. They are, however, in many respects caught between a rock and a hard place While they don't always get it right, they are trying to do the right thing.

Joshua Lederberg, the recently deceased Nobel Prize once observed that the failure of regulatory legal and political institutions to integrate scientific advances into risk selection and assessment was the most important barrier to innovation in public health. Lederberg noted that in the absence of such changes, "The precedents affecting the long-term rationale of social policy will be set not on the basis of well-debated principles, but on the accidents of the first advertised examples." And I can't think of a better place to start a conversation on regulatory oversight on opioids than with that quotation.

Policies and regulations that seek to limit risk are often shaped by the immediate fear of sensational events. This perspective is commonly referred to as the Precautionary Principle, which, in various forms asserts that unless innovators can demonstrate that a new technology is risk free, it should not be allowed into the marketplace. Moreover, any product that could possibly be dangerous at any level should be strictly and severely regulated. But precaution is not always safer than the alternatives.

Let me mention some current examples of precaution in the public health relative to the topic of this meeting. The National Action Plan for Adverse Drug Event Prevention, announced on February 4th in the Federal Register, outlines a comprehensive strategy to reduce AEDs for opioids. Much of the research actions called for by the plan seem designed to decrease prescribing. For instance, the plan calls for research by CDC, NIH, and Public-Private Collaborations to look into adopting adjunctive and behavioral modalities to augment and reduce opioids for chronic pain. The issue of upscheduling and relabeling of medicines to treat depression, diabetes, chronic and acute pain. The role of tamper-resistant technologies in the management of pain both innovator and generic, and an FDA plan on potential class-wide REMS.

Pierre Trudeau once said, "There's no place for the state in the bedrooms of the nation." But what's the appropriate place for the state in our nation's pharmacies and medicine chests? Consider the DEA's thug regulation strategy that results in the decline in appropriate

patient access and increase in regulatory time and cost, and ultimately, a decline in innovation.

The California Medical Association has received reports from physicians that Walgreen's pharmacists are refusing to fill controlled substances without additional information from the prescriber. Per dictates from the DEA, Walgreen's pharmacists are now demanding that physicians provide information on diagnoses, ICD-9 codes, expected length of therapy, and previous medications tried and failed. In other words, tighter restrictions for patients who really need the medications, more paperwork for physicians, and a heavier workload for pharmacists. Alas, abusers and criminals rarely follow regulations. When you have a hammer, every problem looks like a nail.

The DEA sees opioid abuse and seeks to minimize access to them. That's a law enforcement solution. They mean well, but are behaving like a bull in a china shop. Arbitrarily limiting choice is not generally associated with the scientific method. Should regulation be shaped by factors other than science? Or should advances in medicine and digital information be used to right size regulation reduce the excessive reductionism that leads to regulatory overreaction and promote resilience rather than ever increasing regulation.

Consider the program recently instituted by CVS and detailed in a recent New England Journal of Medicine perspective piece, where the use of "Big Data", the chain pharmacy identified outlier prescribers and took appropriate and responsible action. It's an article that I suggest everybody read. The DEA's attempt to deputize pharmacists on the one hand and the CVS program on the other raise some interesting questions. What will the role of the 21st century pharmacist be in improving drug safety and medication adherence via more proactive and remunerated patient education? How can pharmacists become better integrated beyond Med Guides into the FDA's Safe Use of Medicines initiative? When will pharmacy synchronization really kick into gear, and how will states help to jump-start these important initiatives?

To paraphrase the American political scientist Aaron Wildavsky, we at the Center for Medicine in the Public Interest believe in a strategy of resilience based on experience. We must learn from adverse consequences in order to develop a capacity to advance the public health. Variability is the key to survival.

Thank you.

Douglas Throckmorton:

Thank you for the opportunity to share what I had intended to speak about at the conference, and please allow me to extend my apologies for my absence. Coincidentally, I wasn't able to attend because FDA made an important announcement that day about requiring class-wide labeling changes for ER/LA opioid analgesics to more clearly describe the risks and safety concerns with these drugs. We're hoping these changes will encourage more appropriate prescribing, monitoring and patient counseling practices. We are also requiring new postmarketing requirements to better assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death related to the long-term use of these medicines.

On October 24, 2013, we also announced FDA's intent to recommend to HHS that hydrocodone combination products should be reclassified from Schedule III to the more restrictive Schedule II. This determination comes after a thorough and careful analysis of extensive scientific literature, review of hundreds of public comments on the issue, and several public meetings, during which we received input from a wide range of stakeholders, including patients, health care providers, outside experts, and other government entities.

We understand that for the millions of Americans experiencing an acute medical need or living with chronic pain, opioids, when prescribed appropriately, can allow patients to manage their pain as well as significantly improve their quality of life. However, we have also become increasingly concerned about the abuse and misuse of opioids. We are challenged with determining how to best balance the need to ensure continued access to patients who need these medications while addressing concerns about abuse and misuse.

FDA's role in maintaining this balance goes beyond just regulation. We actively engage in regulatory issues, but also lead and are involved in efforts in education and scientific and collaborative activities. Some of these include the work done by our Safe Use Initiative on proper disposal of medications; improving prescriber education by through Risk Evaluation and Mitigation Strategies (REMS) to reduce inappropriate prescribing, misuse and abuse; collaborating in the creation, testing, and sharing of a model Patient Provider Agreement and supporting research into opioid use.

Another important step towards the goal of creating safer opioids, and one that is a high public health priority for FDA, is to encourage the development of formulations of these drugs that deter their abuse. This relatively-new science of abuse deterrence is exciting and evolving and showing encouraging promise. To guide drug development in this

new field, we also issued a draft guidance for industry in January, announcing a flexible, adaptive approach to encourage the development of abuse-deterrent opioids. We believe abuse deterrent products have promise to help reduce prescription drug abuse and improve public health.

All of these efforts are pieces in a much larger effort to promote appropriate prescribing and appropriate use. As we look to the future, we will continue to engage with the many groups active in this area – advocacy organizations, patients and family members, Congress, healthcare providers, and other federal government partners.

### **Advocates, Experts, & Industry**

Steve Usdin: Peter Pitts always puts me in the mood for alliteration. So I'm glad that we have perspectives from patients and policy and Pharma. As Peter mentioned, in any discussion of anything having to do with medicine and especially a topic like pain, the critical perspective has got to be the patient. Everything has to center around the perspectives of the patients. And I'm really glad that we have Cindy Steinberg here whose experience with pain led her to become an advocate and a spokesperson for the US Pain Foundation. And I think I'll let her tell her story herself over the course of the panel. And Bob Twillman. He's at the American Academy of Pain Management. Dr. Twillman received a Ph.D. in Clinical Psychology at the University of California Los Angeles and has focused his whole career on pain management. He's a director of Policy and Advocacy for the American Academy of Pain Management and has a number of academic appointments involving pain and involving clinical management of pain. So I want to start with Cindy ask you to kind of set the perspective from for the patient perspective.

Cindy Steinberg: Thank you, Steve. I want to take a look at what the CDC has been talking about in terms of numbers of people involved in abuse and opioid overdose deaths, and then other comparisons that we might make to those numbers.

According to the CDC in 2008, there were 14,800 opioid overdose deaths. Half of those, the CDC has claimed, involved opioids and other illicit substances, whether it's cocaine or heroin, or alcohol. They also mentioned that alcohol was involved in many of those deaths but they don't actually tell us the numbers. So conservatively, half or 7,400 deaths occurred in 2008 from opioid overdose. The same year from CDC's own statistics, there were 36,500 suicides. There

also were 24,000 alcohol-induced deaths and that doesn't count other related alcohol deaths like drunk driving. So my question is: why aren't these considered epidemics?

The opioid numbers do not even come up in the CDC's list of the top 15 causes of death of Americans. Why aren't we calling for greater restrictions on alcohol? As my friend Bob said, "We tried that and it didn't work." Let's look at some more recent data. In 2010, the opioid overdose deaths were 16,600, but the same year there were 25,600 alcohol-induced deaths. If you look at the numbers for males alone, alcohol-induced deaths are twice that of opioid overdose deaths. The female numbers are about the same. And also there's a little caveat that potentially half of those reported opioid overdose deaths, again, were from a toxic combination of alcohol and other substances including illicit drugs like cocaine and heroin. So, we've heard about the opioid overdose epidemic. We've seen the alcohol numbers. But, what about numbers of Americans living with pain? Those numbers are really staggering.

The recent IOM report that was issued in June of 2011 found that 100 million Americans are now living with chronic pain. That's a third of the U.S. population. Ten million of those have pain so severe that they are disabled by the pain. *Ten million*. The report also said that pain costs the U.S. economy about 600 billion dollars a year in lost productivity and healthcare cost. I think anyone would agree looking at those numbers that this problem is really enormous. Liberal prescribing has been blamed for the misuse and abuse of opioids. But an alternate explanation could be pain prevalence when we're talking about numbers this large. And our population, as we all know, is aging bringing with it age-associated conditions that produce pain like diabetes, cancer, arthritis, musculoskeletal conditions and back pain. We also know that the U.S. population is on a course to double the number of adults 65 and over in the next decade.

Let's look at the issue of chronic pain and opioids. Opioids do not help everyone that has chronic pain. And for those it does help, many still live with significant levels of chronic pain. But for millions of Americans, they can make the difference between a life worth living or not. Pain really devastates lives. It robs people of their ability to work, to earn a living, to socialize and to maintain relationships with family and friends. I often say that it's like being sentenced to a life in prison. You're a prisoner in your own body. But it's worse because you're being subjected to torture 24/7. I know, because about 15 years ago, I had a severe back injury in which I was crushed and every day of my life for the past 15 years I've lived with pain. After trying a lot of different treatments and having not much success, my doctor finally

convinced me to try an opioid combination medication. And for 10 years, I took that medication and it gave me the ability to still be productive. It didn't totally take away my pain, but the constant burning and stabbing neuropathic pain that cut across my thoracic back where I was struck subsided enough that, I could at least function. During that entire period when, I took hydrocodone combination medication, I never became addicted and had very few side effects. The medicine just allowed me to be upright for periods of time and function.

The vast majority of people who use opioids do so legally and safely. A subset, approximately four percent, use these medications illegally. And interestingly enough, the CDC hasn't mentioned that that number has pretty much stayed the same over the past several years. In fact, in 2010 to 2011, the number of Americans misusing and abusing opioid medications declined from 4.6% to 4.2% - it actually *declined*. But we don't hear about that data. Pain medications now and in the past few years happen to be the drugs of choice for those who seek to abuse. But when they're almost entirely removed from the market, as it looks like the direction we're heading, abusers are going to move on to the next popular medication. I was just reading in the paper the other day, that an illicit drug called "Molly" is popular at nightclubs in Boston and has led to overdoses. Who knows what it'll be but we will be leaving people with pain without options, people that really depend on these medications.

Peter was alluding to the current environment that we're in and what it's like for people with pain. There have been some very heavy-handed drug enforcement actions that have led to severe restrictions in access to treatment such as Walgreen's Good Faith Dispensing Policy. There have been, as we all know, highly publicized celebrity overdoses on toxic combinations of drugs, both illicit and licit. It's now created a climate in which doctors are actually afraid to prescribe even for their long-term patients. The U.S. Pain Foundation has approximately 38,000 members. We've been hearing from many of them who have gone to their pharmacy to pick up their medication and they have to wait until their pharmacist can actually speak to their doctor before the pharmacist will dispense their medicine. How many of us ever get to speak to our doctors on the phone during the day? Doctors don't have the time.

One irate doctor in Chicago wrote us that he couldn't possibly answer all the phone calls for his patients and he's a primary care doc. And so people need to wait to get their medications. These are people that are depending on that medication to have any quality of life. It can even cause people to go into withdrawal because like many medications,

opioids can cause physical dependency. That doesn't mean you're addicted. If you suddenly stop, taking your medication, you'll likely have physical symptoms. And that's what's happening to people with pain. So pharmacists are now being told, "Don't dispense, be sure when you do, you've asked the doctors all these questions about what the therapy is, what the diagnosis is and what else the patient's tried." Walgreen's pharmacists are now being told to do that. And many of them haven't been happy about it, but it's a requirement now. In some cases, people with chronic pain are even being denied medical treatment. A nurse practitioner who serves with me on the Massachusetts Pain Initiative Board, actually sent me a picture of a sign in an office in Springfield that said they'll no longer treat chronic pain patients. As Peter mentioned, cutting off the supply of pain medication by enacting restrictive regulations and legislation is not going to solve the abuse problem. As I said before, it will just shift to another medication. We've seen some of that in the uptick in the heroin abuse numbers since OxyContin has now gone to only abuse-deterrent. But this will have huge unintended consequences for people living with pain. More people are going to suffer, some will be unable to work or work consistently leading to a decrease in productivity. I know for myself, if I wasn't able take the medication I did for 10 years after my accident I wouldn't have been standing here talking to you and would not have been able to do the advocacy work that I have done for many people that live with pain who cannot advocate for themselves.

I lead a support group for people with pain in the Boston area that now has 300 members. I started that group by hanging up a sign at a local library after my accident thinking I couldn't be the only one that's living this way. And people just started showing up. That was 13 years ago. I do the group monthly. Members range in age from 18 to 85 with a wide variety of conditions that cause debilitating pain such as rheumatoid and osteoarthritis, CRPS also called RSD, migraine headaches, cancer sometimes caused by the lingering effects of chemotherapy treatment, back pain, other musculoskeletal conditions, thoracic outlet syndrome, and diabetes because long-term diabetes often leads to neuropathy. As our population ages we will see a large increase in pain care needs and healthcare utilization due to the prevalence of age-associated pain producing conditions.

Peter also mentioned upscheduling or rescheduling of hydrocodone combination medications which have been proposed in a current bill. That's going to mean that people need to see their doctor at least four and sometimes 12 times a year just to obtain a script because of the very strict requirements on Schedule II medications. The hydrocodone combinations are now Schedule III and if they are upscheduled, in

Massachusetts for example, where Schedule II scripts expire in 30 days and cannot be written for more than a 30 day supply, many people in my group are that are taking hydrocodone combinations medications would have to see their doctor every 30 days for a script. They now see their doctor perhaps twice a year. So, they would have to go see their doctor 12 times per year. People have a hard time finding a pain doctor period, let alone getting an appointment. Somebody in my group was referred to a pain specialist in January of 2012 and the first appointment she was able to get was in December of 2012. She had to wait almost an entire year to see a pain doctor. So how are we going to handle the number of people that are going to need appointments to get their medications? In Massachusetts, as I mentioned Schedule II scripts expire in 30 days and by federal law cannot be refilled. I have a person in my group that has osteonecrosis. He was an early heart transplant patient and the steroids he had to take to maintain his organ transplant resulted in osteonecrosis which has eroded every joint in his body. He's had multiple joint replacements and lives with a very high degree of pain. His wife has to drive him to the doctor now every 30 days in order to get his Schedule II medication because he needs to get a physical script. And that's going to happen to many people if these Schedule III medications are rescheduled. And as I mentioned, given all those extra appointments, think about what that is going to do to healthcare costs. There are many more equitable, balanced solutions to this abuse problem. Education about securing medications, requiring lock boxes in pharmacies, which we've done in Massachusetts recently, encouraging the development of tamper-resistant and abuse-deterrent formulations and more education for kids as young as middle school on the dangers of abusing these medicines. We have a pilot program in Massachusetts now for middle school students that was also in a recent piece of legislation that we passed. Establishing more frequent or even permanent take-back programs for unused and expired medications is another important step we could take. The DEA Take-Back Programs have been incredibly successful. Photos from these events show millions of unused bottles of medication that are sitting out there in people's medicine chest.

Reimbursement for multimodal treatments for chronic pain in addition to pharmacotherapy is another important avenue that should be pursued. Pharmaceuticals are certainly not the only way to manage pain. Successful pain management usually requires several different modalities in combination such as exercise, cognitive behavioral therapy, physical therapy, massage and many others. Many of these are not reimbursed. Chiropractic and acupuncture in some cases are starting to be covered by insurance but for the most part these types of treatments are not well reimbursed. And of course, promoting

research directed at identifying who is likely to have a substance abuse problem and who can function well on these medications is critically important. We're going to hear more about that in terms of personalized medicine later today. But it's very clear that there are many people that do well on opioid medications and there are some people that don't. We need to get a lot smarter at identifying those that don't rather than using a broad brush measure that will significantly harm the many living with pain who depend on these medications to live a functional life. Thank you for listening. I think Steve is going to ask some questions.

Steve Usdin: Thanks. I'm going to ask all of my panelists an opening question and then we're going to have it open for discussion.

Stuart Kim is Associate General Counsel for Regulatory Affairs at Mallinckrodt Pharmaceuticals. The company is one of the largest manufacturers of pain medicine in the United States, maybe the largest. I think that the question I had that kind of want to- in lieu of an opening statement was really to ask you, you know, in order to solve these problems, everybody who's a so-called stakeholder, you know, patients, physicians, regulators, and companies are all- all have a role to play. They're all going to have to change their current behaviors. So to start with, I wanted to ask you, what do you think of the behaviors of drug companies? What do they have to change in order to improve access to pain medicines, to reduce abuse, and to prevent overdoses?

Stuart Kim: This is an incredibly complex public health problem. And there isn't going to be one solution, one activity, one program that's going to solve or probably address this issue. And I appreciate the conversation this morning so far in which we are really balancing two competing concerns.

One is we want to make sure that patients with pain have access to these medications that they need but then we also have to address the concern of managing risk, not eliminating risk but managing risk of opioid abuse. And so, two competing concerns, very complex. For manufacturers like Mallinckrodt, we are definitely a stakeholder in this discussion and we can't do this by ourselves and so we have to collaborate, we have to cooperate with all the other stakeholders. But from a manufacturer's perspective, we as a company have worked toward and have supported five different components that we think will help address this issue of opioid abuse.

One, of course, is encouraging the development of abuse-deterrent formulations for opioids. And I think the best way to do that and I

know the FDA is working toward this is to establish and communicate clear and fair regulatory approval standards for both brands and generics so that we have some level of regulatory certainty as to how we can go about formulating and what is expected of us as a drug company.

Second is to improve our state prescription drug monitoring programs. We have I think a very robust set of state, individual state programs. But I think one is funding that we need to make sure they continue to be funded. But there needs to be a level of interoperability now. Communication, real time data sharing between states, so that we have one particular non-patient who gets a script in Florida and doesn't go to another state to try to get that filled. That's the value I think of the state PDMPs.

The third component goes to this idea of establishing and implementing best practices for what we call SOM, Suspicious Order Monitoring. What is this? At the manufacture and the distributor level, we look at signals if you will, of where our products go and we stop those particular orders where there appears to be some type of unusual activity, what we call suspicious orders. And we stop the flow of controlled substances to that particular distributor or pharmacy.

Fourth is that we advocate for drug take-back programs. We think they are extremely effective. We think they are worthwhile. And I think there's a need based on the feedback we've received from people who participate in these programs that they need to be available nationwide.

And then lastly, goes to this idea of education and training which many of you have probably heard through various channels. We've taken a slightly different position in that, yes, we do encourage education and training but there has to be a goal and an end in mind. And what do I mean by that? We're looking at something toward what we call better measurable outcomes. Have the physicians changed their prescribing behavior, have the patients actually responded better to the treatment. Are they able to ambulate after? Are they able to leave the hospital quicker? Those types of measurable outcomes need to be tied in with any type of training that we give to healthcare professionals, which includes physicians, nurse practitioners, and pharmacists. So, those are the five things that I think manufacturers like Mallinckrodt need to support, need to think about, and need to advocate for as we look forward to this to solving this opioid abuse issue.

Steve Usdin: We've already referred from the patient respectfully from industry drug drug industry perspective, you know, it's no accident that we're on Capitol Hill. Bob, I wanted to kind of put you on the spot and ask you, to talk a little bit about what do you think are the policy levers that Congress should be using to try to address the issues that we're talking about today?

Bob Twillman: Sure. I think there are numbers of things that Congress can be doing and other agencies and the federal government as well to help us solve this problem. There are a couple of pending pieces of legislation right now that I think are really promising and they're part of the solution to this problem. There's the Stop Act which is H.R. 486, which really focuses on tamper-deterrent formulations and the continued development of those. That's something we very much support. We recognized that's not going to solve the entire problem. People can still abuse medications by swallowing intact units. But for those who crush them and then snort the drug or inject it, the tamper-deterrent formulations can be life savers. So we think that's very important. Senator Boxer has a bill, it's Senate Bill 1277. And what that bill would do is to establish a commission to bring all of the stakeholders together to have discussions about how to approach this issue so that you get law enforcement and providers, and patients, and pharma all at the table together to talk about solutions that work for everyone. Because too often I think what happens is that the conversation tends to get dominated by the most shrill, the most- the people who have the most egregious examples to present. And I think that that oftentimes makes for bad policy when you look at the worst cases and you don't include all of the stakeholders.

Continuing to push on the DEA rule making process so that we can establish regular take-back programs, very important. What the data from SAMHSA(**Substance Abuse & Mental Health Services Administration**) tell us is that about 70 percent of people who misuse prescription opioids tell us that they get those medications from friends or family, either they're given them for free or they steal them out of medicine cabinets, or they're sold by someone, and to find ways to keep those medications from just sitting around for years so that they're available is really, really important. So I think continuing to push on that process and getting through that is something that's going to be important.

Stuart mentioned the Prescription Drug Monitoring Programs. And certainly, we think those are also extremely important tools, 49 states had passed legislation to establish those. I've personally worked in Missouri for the past three years trying to get them on board and I'm not sure it's going to happen again this year, but nonetheless, we're

going to continue to work on that. And it's a very important tool for us. So, the federal government has been involved a little bit in sort of looking at what's next for Prescription Monitoring Programs. SAMHSA has worked with the Office of National Coordinator. And last summer, they came out with a big report on how to do these emphasizing things like the importance of integrating Prescription Drug Monitor Programs with electronic health records and health information exchanges. Because right now when a prescriber wants to check on a patient's PDMP report, they may be working on the computer in the patient's electronic health record. To check the PDMP, they have to close down that program, open another program, obtain the PDMP report, download it, get back into the electronic health record, and compare all of the information there. It's really very unyielding and it's very time consuming. So one of the initiatives that was recommended by the ONC is to find ways to integrate these programs so that when someone opens up a patient's electronic record, they not only get the information that's there because other providers have entered it, but it also automatically loads the information for the PDMPs. There have been some trial programs doing that and it's worked out very nicely. So we now know how to do this. Now, it's a matter of taking it to the next step and making it happen. So doing things like that are going to be very important.

We think also the government needs to focus a little bit on the demand side of this problem. You know, prescription drug abuse is in some ways like the typical economic problem, it's got both a supply side and a demand side. Law enforcement, as Peter mentioned earlier, has really been focusing on the supply side. Let's reduce the supply of these medications and then people won't abuse them as much. Well, you know what? That's what we've been doing for the last 40 years in the war on drugs in this country, is working on the supply side. And what we see is what we call the "squeezing the balloon effect". You clamp down on supply in one area and you get a bulge in another area. So in the '70s, we clamped down on heroin, and what do we get? We got a bulge in cocaine. So we clamped down on cocaine, and what do we get? Now we get a bulge in prescription drug abuse. And as we clamp down on prescription drug abuse, what are we seeing? A rebound in heroin use. So it's silly. We just keep shifting the drug that's the focus.

What we need to do is let the air out of the balloon. And we let the air out of the balloon by providing better and more effective treatment for people who have an opioid addiction. So we need the government to take steps to make addiction treatment more available to people, to make it available in wider areas, and to encourage people to engage in that kind of treatment. So we really have to begin addressing the

demand side. You know, in general, I think we need policy makers to sort of back up the talk a little bit because I hear talk all the time about people saying, "Well, we have to be sure that patients still have access to these medications that they need." But when solutions get proposed, they're really very blunt instrument solutions that run the risk of impending access for patients as well. So everyone talks about how as the amount of medications that's prescribed has increased, so have the number of overdosed deaths. And so the solution that's proposed is let's reduce the amount of medication. Well, you know, there's a saying that a rising tide floats all boats. So as we've had an increase in the prescribing of opioids, we've had an increase in the number of people who use those to treat their pain. We've also had an increase in the number of people that use them for purposes of abuse. As we'd lower the supply, we're going to see both of those groups affected. It's sort of the opposite of the rising tide floats all boats. It's like an ebbing tide lowers all boats or something. And that's what—that's what we're concerned about.

It's interesting that we hear about the sharp increase in the number of people dying of overdose is involving prescription drugs. But at the same time, there was a data just released last week from SAMHSA. Every year, they do this survey called the National Survey on Drug Use and Health where they estimate the number of people who engage in non-medical use of prescription opioids. That's a question they've asked every year since 2002. And you know, the rate in 2012 is exactly the same as the rate in 2002? For the last decade, there has not been an increase in the number of people misusing prescription drugs according to that survey. Yet, the number of people dying is increasing sharply. So what's happening? It's not that more people are dying because more people are misusing. What's happening is more people are dying because people are misusing more. Or they're misusing in different ways. And to back that up there's a study it was done by Chris Jones, he's a pharmacist at CDC. And what he did was to examine these data a little more closely.

Over a period of time when the increase in the number of opioid overdose deaths was 94 percent, there was a 74 percent increase in the number of people who reported misusing opioids more than 200 days per year. So, if we want to have the fastest and the greatest impact on prescription opioid overdose deaths, what we need to do is to find these people who are already misusing and intervene with them. That's what we've got to do, is to train healthcare providers to detect these people and then to provide appropriate treatment for them. And then one final issue that Cindy alluded to a little bit which is the issue of hydrocodone rescheduling. Many of you may know that that's something is under consideration by FDA. They had an advisory

committee meeting audit in January and the advisory committee voted 19 to 10 in favor of rescheduling hydrocodone from Schedule III to Schedule II. Well, what I found interesting was a number of the comments by members of the panel as they went around and explain their votes. Many of them said, "You know, we feel stuck here because we're given the option of saying 'Yes, reschedule,' or 'No, don't reschedule.' And we wish we had a third option." Because the trouble is we're not sure that this is going to solve the problem. There are two prescription opioids that are essentially equally abused, oxycodone and hydrocodone.

Oxycodone is already in Schedule II. So the evidence doesn't necessarily suggest that moving something into Schedule II reduces the abuse of it. So panel members were concerned that this move is not going to have the desired effect. And they really- many of them said "We wish we had a third way forward." Well, we've been advocating for that third way forward. And it's something I want to toss out here and see if it gets some traction. We think that it's entirely impossible to maintain better control over the supplies of the medication, appropriate controls without causing a lot of unintended consequences. And the way you do that is you keep hydrocodone products in Schedule III, but you change the rules for prescribing Schedule III medications just a little bit. So first of all, right now, you can call in a prescription for hydrocodone products, for Schedule III product. And effectively, a prescriber can pick up a phone and call in a six-month supply for a patient. What we'd like to see is that there will be a limit placed on the amount that can be called in. Called in prescriptions really should only be used in an emergency situation to get the patient to the doctor's office so that they can be examined, and a proper diagnosis made, and proper treatment decided on. So limit the amount that can be called in to just a short supply, maybe a maximum of seven-day supply. And then limit the amount that can be given with the original prescription plus refills to a 90-day supply. Right now, it's 180 days. There's a technique that can be used with Schedule II medications where a patient could be sent home with three prescriptions each for a month supply. But they have to be written in a particular way. And the trouble is that once those three prescriptions leave the doctor's office, there's no getting them back. There's no stopping the second prescription or the third prescription from being filled because the patient can take those three prescriptions to three different pharmacies. If you have refills on a prescription, what can happen is if the doctor sends the patient out with this prescription with two refills on it, the patient takes it to the pharmacy, fills the prescription, and then the doctor learns something about the patient that makes them not want to be- not want to have them get the second and third prescriptions filled. They looked the patient up in the

Prescription Monitoring Program, find out which pharmacy has the prescription, and they call the pharmacy and cancel the refills. So it's the same amount of supply that you get with Schedule II, but it actually has greater control over the medication than the current situation.

There were 26 million refills of hydrocodone products last year. If hydrocodone gets rescheduled, we're going to have to find room in our healthcare system for 26 million more appointments for people to get their refills taken care of. And I don't know about you, but my doctor's office has got a pretty long wait and I don't think we can add 26 million additional visits. Furthermore, think about the cost of that. If the reimbursement is say 30 dollars for each of those visits, we're talking about 780 million dollars a year just for all these additional appointments. And Medicare and Medicaid is going to suck up about a third of those. So, at a time when everybody is worried about the budget, here's something that's going to increase cost, make people access problems worst. And maybe not even solve the solution, not even solve the problem. And the final piece of this, the thing that's important about keeping these medications in Schedule III is if they're moved to Schedule II, all the wholesale distributor is going to have to remodel their warehouses to increase their secure storage areas, to secure what is actually a huge volume of medication. Retail pharmacies are going to have to expand their volts that they keep their controlled substances in because Schedule IIIs don't have to be in those volts but Schedule II do. They're going to have to do daily inventories of all those medications that now they don't have to do that. So it's going to be an extremely expensive proposition for wholesale distributors and retail pharmacies. And guess who's going to pay for that? It's going to be you and I because they're going to charge more for the medications. So by keeping in Schedule III, we avoid that unintended consequence, too. So that's something we'd like to see get a little bit more discussion, a little bit more traction, there's a possible third way forward.

The elegant thing about it, that doesn't even require legislation. All it requires is some DEA rule making for that to happen. So we don't have to get this pass through Congress. We're concerned about Congress legislating because they don't like what DEA or what FDA has decided anyway. We think the FDA engages in a thorough careful scientific process and it's probably not Congress' place to overrule that. So if we consider this alternative, we think that maybe we can solve the problems without creating more. With that, I think I'll stop and see if folks have some questions some of the discussion.

Steve Usdin: Why don't we pick right up on that because it's an interesting idea and kind of interesting in hearing what Cindy says about it because one of the things that you emphasized was the difficulties it causes for patients to have restrictions on access, to have to see physicians more often, something like that. So we're interested in, you know, what your perspective on that proposal is and also, Stuart, what your reaction as a manufacturer.

Cindy Steinberg: I guess I'd have to disagree with Bob on that one issue. I really don't believe that rescheduling hydrocodone combination medications will solve any of the abuse problem. What it will do is make it much more difficult for people with pain to get their medication. I will use myself as an example because I used a combination product for 10 years. I've since found a different medication that's more directed at my nerve pain. But in my case, over a 10-year period, I took this medication and it enabled me to function and lessened the daily burning, sometimes stabbing pain across my back. My doctor had to convince me to try it rather than withstand the pain. I had no problem with abuse. In fact, I took too little of it. I was too scared to use it thinking "Oh, my God, it's going to do something terrible to me." He knew it was helping me to participate in life and be functional again and eventually I only had to see him once a year and he was able to call in refills for me.

I know how to manage my pain. I do it with the combination of limiting the amount and time I'm upright. I do a regular exercise program including a water-based program and I take medication. And that combination of things keeps me functioning. So if I had to go to my doctor every 30 days just to get a script, or as Bob has suggested, every 90 days, that would be at minimum three additional appointments a year that I don't need. Why would we want to clog an already overburdened healthcare system which this proposed rescheduling will certainly do? So, I feel pretty strongly that the combination hydrocodone medications should remain where they are, in Schedule III.

Steve Usdin: And maybe that tradeoff that Bob was talking about is not that the option is to keep it where it is, or to have this kind of added restrictions. He's saying- He's basically suggesting that the choice is it's either going to get rescheduled to Schedule II or Schedule III is going to be modified. And if you're looking at that kind of a choice, where would you like? I mean, is that stating what you're thinking?

Bob Twillman: Right. That's our concern is that if the FDA decides not to reschedule, that there's going to be some pressure to pass two bills that are already in the hopper, one on the Senate side and one on the House side that would reschedule. And so, as an alternative to rescheduling, that's

what we're proposing. We're not proposing this necessarily as an alternative to the status quo. But if the choice is either rescheduling or this alternative, we think this alternative is much preferable.

Steve Usdin: And Stuart from your perspective.

Stuart Kim: Bob, I think you hit on some very important issues and topics that we as a company and as an industry are concerned about as well. As a manufacturer and as an industry, I think we are going to adapt to whatever comes down from FDA, DEA, and Congress. But we are very concerned again about these issues of patient access, again trying to address two competing concerns. And so whether it be rescheduling, whether it be PDMPs, and we are monitoring, we're watching and, you know, we are looking toward partners such as both Cindy and Bob to advocate for the patients to make sure that they have access to opioids.

Steve Usdin: I'd like all three of you to talk about abuse-deterrent technologies in a couple of perspectives. One, it's obvious as somebody said, we didn't solve the problem. The question is how important are they and what are they like from the patient perspective, and from the manufacturer's perspective especially and from a policy perspective, one of the kind of conundrums about abuse-deterrent technology, I think involves generic drugs and the idea that if you have branded drugs that use an abuse-deterrent technology, if it's effective, should those technologies be mandated for generics, if they're not, then what's the point because the market will be flooded with the generics and the deterrence won't be deterring. Who wants to pick it up first?

Bob Twillman: Well, as luck would have it, I actually wrote a position statement about tamper-deterrent formulations last week. So, you know, I think, again, they are part of the solution. They're not the whole solution. And I think that for some patients, they are absolutely necessary. They can be lifesaving measures. I think what needs to happen in the system and then we have to figure out how to make this work policy-wise is that when a prescriber sees a patient, they need to do an assessment of what's the risk involving this patient, either the patient is going to tamper with the medication and potentially expose themselves to some danger. Or that someone in that person's social milieu, their grandchild or the worker who comes to the house and asked to use the bathroom or, you know, whatever, has potential to access that medication and tamper with it and cause some problems as well.

Steve Usdin: I'll stop you right there. Is that realistic? Can physicians make that kind of determination?

Bob Twillman: Within reason. You know, you can look at certain factors and make a determination that some patients are at higher risk than other patients. The trouble is it takes a little bit of time to do that. And, you know, physicians are preferentially reimbursed for turning the room over as fast as they can. You know, it's interesting this a little bit of an aside. But the reimbursement for office visits is a little bit perverted in this area because you get X dollars for the first say 15 minutes with the patient. For the next 10 minutes, you get X minus Y dollars per minute. And for the next 10 minutes after that is X minus Z dollars per minute. So actually for patients who are more complex require more time, you actually get paid less to spend more time with them.

Stuart Kim: That's right.

Bob Twillman: So it's a perverse reimbursement system that really encourages people to spend as little time as possible with patients. So in any case, if you make that assessment, then you can decide is this a patient who really would benefit or who I think, would I feel safer prescribing a tamper-deterrent formulation or not. Those who the prescriber intends to have tamper-deterrent formulation need to get the tamper-deterrent formulation. So one of the pieces of legislation that's been floating around at the state level, I don't think it's been adopted in any place yet, is legislation that would prohibit the automatic substitution for a tamper-deterrent formulation of a non-tamper-deterrent formulation generic. As many pharmacy benefit managers are going to want us to substitute these non tamper-deterrent generics because they're a lot cheaper. But if the prescriber intends for that patient to have that medication, then we think they need to get that medication. By the same token, we don't think patients who've been on these medications and are using them 100 percent appropriately have no increased risk should be penalized by having to pay more money for those medications. So we think that there needs to be a way for patients who don't need tamper-deterrent formulations to get medications that don't have that tamper deterrence in them. Or to get adequate reimbursement for their tamper-deterrent formulation that are out there.

So it's still a problem we're working through a little bit and trying to figure out how to do this. You know, so, we certainly favor the development of more of these medications. We think they need to be available and someone intends for a patient to get them, they need to get those medications, but we also need to find a way to pay for them so that patients aren't penalized when they don't need those medications.

Steve Usdin: Stuart.

Stuart Kim: I think from a manufacturer perspective, three points I think. One is we as a manufacturer because Mallinckrodt manufactures both brand and generic opioids, we have this regulatory uncertainty and we need to have some more clarity. And I know the FDA is working hard on this. But what are the regulatory approval standards to incorporate such technology into a brand or a generic formulation. I think that's one.

Second is we as a company believe we want to have these abuse-deterrent formulations as options for practitioners to add to their toolbox so that they have more choices to better treat their patients.

And then lastly, from a company perspective, what we're striving for in pursuing and investing in these abuse-deterrent formulations, we still want to offer and provide safe and effective medication when used as direct and as approved by the FDA, but also to have characteristics that will discourage those non-patients from seeking Mallinckrodt products. And that's- then what we're trying to do philosophically from a formulation and from a development standpoint as it relates to abuse-deterrence.

Steve Usdin: Cindy?

Cindy Steinberg: I would agree with both of the panelists. And I think it's very important that we encourage abused-deterrents but I agree with Bob in the sense that I think that decision should be left with the prescriber. I would add one more piece which is prescriber education. So in Massachusetts, we worked very hard to put in place a requirement that doctors must have three hours of continuing education units in pain management and substance abuse every two years in order to renew their professional license. I just attended one of the trainings that Boston University Medical School ran about a month ago and it was excellent. The course teaches doctors how to better stratify their patients, so they understand who might be a candidate for the abuse-deterrent medications and who isn't. And as Bob mentioned, we don't penalize people that would never abuse the medication. At the same time, we take careful steps to make sure those that might don't get into trouble. So that's what I would recommend.

Steve Usdin: Stuart, you mentioned an idea kind of accountability or metrics in training and you gave the example of whether physicians- patients are getting out of hospital sooner or having their pain maintained sooner, is there another set of metrics. Does it make sense to tie continuing medical education to measures of some kind of measures that would

indicate that physicians aren't prescribing it appropriately or that their patients aren't overdosing, or aren't becoming addicted?

Stuart Kim: With regard to continuing medical education, this is something that I know is being looked at, at the federal level and the state level. But CME has been around a very, very long time. But I think we need as stakeholders to look at sort of a new paradigm which is this idea of quality improvement. So you have a physician attending a three-hour session, right, and hopefully it's very interactive, they're very engaged. The question then becomes has that physician actually changed the way he is looking at patients and evaluating them, doing the appropriate assessments. And what is actually happening after he does that? And so, this is what I'm talking about with regard to outcomes. The best analogy I can give is sort of looking at the clinical trial. You go in, you develop a clinical trial, and you have endpoints as to what you're going to measure to make sure that the study meets its goals. CME needs to be looked at in a similar way in terms of a quality improvement perspective in that, you say, all right, we're going to have these objectives and the FDA has tried to do this with the class-wide REMS. These are the objectives. These are the goals that we need to educate physicians on but you need to have something at the end saying, "Did they learn? Did they retain? What did they do to change their practice? And did the patients actually get better treatment, better relief of their pain?" And there are some initiatives, one of which our company has funded, where we are trying to sort of change the discussion a little bit to look at patient records anonymously to work with physicians who've gone through this training and try to really understand how they are looking at their patients, and how they're changing their practices. And this needs to go beyond the three-hour live program. I think it's a starting point. But this is really a continuous improvement where they need to have reinforcement over a period six, nine, 12 months follow up as to what have they learned and how actually are you doing this. So, we're advocating sort of a paradigm shift in terms of trying to get medical education to the next level.

Cindy Steinberg: I think that's a good idea. And I would add that we have to look at medical schools and schools of nursing, and anyone who prescribes, dentistry schools as well. We're really lacking in pain management education. Someone calculated the average number of hours of pain management education in the typical medical school curriculum and it was very low. I think the average was something like 8 hours over a four year curriculum. They are not required to take a course on pain, yet pain is the number one reason why Americans visit their doctors. There's something wrong with that. And I think beefing up the

medical curriculum to include pain management is a really important thing.

Steve Usdin: Bob, did you want to address it?

Bob Twillman: Well, actually that's the other position statement I wrote last week, was about continuing medical education. And, you know, the challenge with requiring it is that we've learned in the past about education, particularly in the area of pain management is, you know, it's something that's necessary because you can't do what you don't know. So we have to educate everyone so they know what to do. But it's not sufficient because it doesn't produce change. So it's a hard call here. You know, it's necessary but it's not sufficient. So we have to have it for people. People have to learn more about how to do this. But how do we ensure that it has the desired outcome? And I totally agree with what Stuart had to say about, you know, looking at the outcome measures, looking at this as more of a quality improvement type of thing. But I think the other thing is, you know, nobody likes to be told that you have to go do this.

Physicians are especially unhappy when people tell them they have to go do something. So how about incentivizing it? Maybe if we have the kind of outcome data that Stuart shows us, maybe then physicians who take that training could pay a little bit less in malpractice insurance premiums. Maybe they get a little extra reimbursement from Medicare or Medicaid or something for patients that they see because they'll be providing better care and more efficient care. But in order to get there, I think we have to have some of these outcome numbers that we don't have so far.

Steve Usdin: I have one more question that I had then I want to come open up for the audience. There are patients who have pain that needs to be treated. There are physicians who want to make sure that their patients get the best. There are drug companies that want to make sure that patients get access to drugs. But there's a reality there which is that everybody in the system, in this problem isn't created by people wanting to do the right thing. There are criminals. There are- you know, the oceans of drugs that are available for people, anybody who has had a teenager and actually had an honest conversation with them and knows what their access to opioids and drugs is, it's terrifying. So there is- there's a real problem about criminals and criminal activity. What needs to be done on that score?

Bob Twillman: Well, I have a teenager and I'll tell you a couple of years ago when I saw a survey come out that said teenagers said it was easier for them to get prescription drugs than it was for them to get beer. I was a little

shocked. And, yes, absolutely, things have to be done to identify the criminals who will take action against them. But, you know, here again, what we see is that so many times, people propose simple solutions to complex problems. And I think there's a statement to the effect that every complex problem has a solution that is simple, elegant and wrong, or something like that. And unfortunately, that's what we see.

One example of this is, you know, Florida passes a bill to eliminate its pill mills. And, you know, it was a tremendous problem that they had with pill mills. But what they did was to come in and say, "Every clinic that calls itself a pain management clinic now has to register with the state. They have to meet higher standards in terms of what they do in their practices. They have to pay 1,500 dollars a year for the privilege of having an inspector come out from the Department of Health to look at what they're doing and make sure that what they're doing is appropriate." So, now what you've done as you've said all pain management clinics have to have increased regulation on them. Well, you know, when you do that, it encourages some people to go out of business. And part of the problem is we don't have enough really good multidisciplinary pain management clinics for all the people who have chronic pain.

We have to find ways to regulate this and to legislate this that don't wind up harming the people we need to have more of. And so, you know, we've been pushing a little bit on this and no, I haven't written a position paper on it, but I did publish an article last summer on this. So, you know, I think we've got to be cognizant of the fact that a pill mill is not a pain clinic, regardless of what sign outside says. We can make the distinctions here. And if we just enabled the medical boards to do their jobs the way they need to, I think we wouldn't have the problems that we've had. I think the solution to these kinds of things lies not necessarily as much with law enforcement as it does with the regulatory mechanisms that we already have. So I'd like to see us find ways to make better use of that to control the problem.

Steve Usdin: Cindy.

Stuart Kim: I agree.

Steve Usdin: A question from the audience ...

Audience Member: In terms of trying to prevent the opioid overdoses, I haven't heard anybody mentioned naloxone. And there has been a good program in Boston where if you prescribed naloxone along with the opioids, it can help prevent a lot of opioid deaths. Why not pursue that a bit?

Steve Usdin: And in answering if you can explain in case there are people who don't understand what that's about.

Bob Twillman: Naloxone is an opioid antagonist and so what happens is that if you take an opioid, you take a bunch of Vicodin or oxycodone or whatever, and it hits the receptors in your cells and begins to suppress your breathing, what you can do is you can administer this medication called naloxone, sometimes also known as Narcan, and what it will do is basically unbind those receptors. It will immediately reverse the effects of the opioids. And it's a very dramatic thing when you see it happened to someone, you know, certainly in my career working in medical centers, I've seen it administered to people and it's a dramatic immediate response when people get a dose of naloxone. So what's been proposed is that this be circulated more widely so that if someone who is, you know, a significant other, if someone who is taking a medication finds that person looks like they're dying of an overdose, they could administer this naloxone and rescue them. And it's actually shown to be very effective.

In Quincy, Massachusetts I think is the place where they've been doing a lot of this. They have well over a hundred documented saves of people. It's also been done widely in North Carolina with something called "Project Lazarus". And Project Lazarus is there's a lot more to it than just the naloxone. But we think it's such a promising model that we're working right now to implement it in Hillsborough County, Florida in the Tampa area to- as a demonstration project. So making this medication more readily available and available in forms where the ordinary person on the street can give it, we think there's also something that's a very effective strategy to reduce the overdose deaths. But then you've got to take the next step and say, "Okay, how do we prevent the overdose in the first place?" The most immediate thing is saving someone's life so that they're not dying from the overdose. But then let's back up another step and let's also look at how do we prevent the overdose in the first place.

Steve Usdin: Another question from the audience ...

Audience Member: I've seen this dance 25 years. It's a very complex situation we have here in pain management. But my question is this, what are we doing for alternative treatment. I know some 20 years ago, we started the multidisciplinary approach to patients. And that seemed to work for a while. But I know when I was in practice, we had- I would titrate patients down off of certain opioids and then just go ahead and put them in the hospital for detoxification. But somehow, they seemed to

have relapsed and they come back. So then we decided that we wanted to do some complementary and alternative treatments like biofeedback and of course, we're still stuck with the conventional treatment of the physical therapy and so forth. But now, it seemed to have gotten worse some 25 years later. We have patients now overdosing on the opioids. And I'm just wondering, what are we doing to see if we can bring some of these alternative treatments onto the scene to see if we can have? Are we doing anything?

Steve Usdin: Cindy?

Cindy Steinberg: People need to use a combination of approaches and they're unique to each person. That's another complication of pain. What helps one person is not necessarily going to help the other. I think reimbursement is very important. I think we need to stress much harder the importance of reimbursing alternative methods of controlling pain like you have mentioned including mind-body approaches such as meditation, relaxation, cognitive behavioral therapy which I mentioned earlier, acupuncture is helpful for many. And people using that combination in concert with various exercise programs would be more successful and likely less costly than many of the invasive procedures that are reimbursed now. There have been some pilot programs as Bob mentioned. Integrating alternative treatments with careful selection of medication and some physical movement techniques are likely to be most successful.

Steve Usdin: Isn't part of the issue on that that you need a lot more evidence around it before payers are going to be comfortable reimbursing for?

Cindy Steinberg: That is true and is why we're glad the NIH now has an alternative and complementary institute which, is doing more rigorous research in this area.

Bob Twillman: So you remember what I said earlier about a complex problem with simply solutions? This is another example of that. Chronic pain is a complex very difficult situation. And the simple solution of writing a prescription doesn't get the job done for many people. Maybe even for most people. There really needs to be a lot more done. And the challenge again is that, you know, each- I sometimes put it this way, that each person with chronic pain that you encounter as a clinician is an end of one experiment. You make your best guess about what's going to be effective and you start that and whether that's a medication, physical therapy, psychotherapy, sending the person to yoga classes, having them lose weight. There are a number of things that you can do to help people manage their chronic pain. But what you do is you put all of this in place as best you can and to the extent

that it gets reimbursed and that is a major challenge. But then you follow up and you make changes to the plan as you see how it's working.

Unfortunately, the major limitation that we have with this is all about reimbursement. So, you know, what gets reimbursed? Well, seeing a patient for 15 minutes, writing a prescription as their ticket to get out of the exam room. Or sticking a needle in somebody and giving them an injection. That's what gets reimbursed. Trying to get an adequate amount of physical therapy for somebody, trying to get an adequate amount of psychotherapy, never mind something like massage therapy or acupuncture that can help a lot of people is a real challenge. And yes, we need more evidence to be able to support the use of those. But, you know, the thing that strikes me in all of these discussions about prescription drug abuse is that unlike 10 or 15 year ago, I don't hear a lot of people saying, "Well, those people don't really have pain." I don't hear that right now. So my question in response to them is, "Okay, if you don't want us to use opioids, what do you want us to use?" Make it possible for us to use all of these other things and we won't need as many opioids. We won't be using them exclusively. So we really have to work on accumulating the evidence and changing the reimbursement policies and the education of providers so that we can take advantage of all those other things.

Steve Usdin: Peter Pitts has a question ...

Peter Pitts: Bob, you talked about DEA ruling, Stu, you talked about FDA incremental predictability. I'm sure you hear about that this afternoon from the FDA. Cindy, you talked about the issue of POP scheduling. What's the appetite politically on Capitol Hill in state houses around the country for incremental regulatory solutions rather than big political statements?

Bob Twillman: Well, you know, what gets votes is the big political statements. And so that's part of the challenge is that there's a lot in the media about the magnitude of this problem and the horrendous cases that people talk about of, you know, teenagers going to parties and taking things, and overdosing, and dying, and so forth. And everybody says, "I've got to do something about that." And so, let me find a solution. And it becomes I think far too often it becomes an exercise of ready, fire, aim, you know? People make a decision to do something. And then discover later that that probably wasn't the right thing to do. It's a real challenge because what sells to the media, what sells to voters is doing something. Just something. Doesn't matter really what it is as long as you're doing something. But if it turns out to be the wrong thing then we've set ourselves back in some cases. And it is a major challenge

trying to get people to look at this and take that incremental approach that I think is what we really need.

Stuart Kim: But I think the fact that we're here, I think that conversation is now really starting to occur and I think there are very thoughtful legislators at the state and the federal level who understand- they want to do something. So that motivation is definitely a positive, but then the question is do what?

Bob Twillman: Right.

Stuart Kim: And so, again, I think this briefing is the starting point for that very difficult conversation.

Cindy Steinberg: I think it's a good point that there are regulations but it needs to be done intelligently. And one of the things we've done in Massachusetts is establish a joint policy workgroup that's working within the DPH to get all stakeholders at the table and talk about how to attack this problem. Senator Boxer's legislation would do very much the same thing. With a complicated problem like this, we need everybody involved to get their heads together about what's the best thing to do. So we support Boxer's legislation to establish a commission. And like I said before, we got our lawmakers when they first introduced this very troublesome bill that included rescheduling, another piece of this bill that luckily did not become law was targeting the top 30 percent of prescribers in Prescription Monitoring Program for extra surveillance. Who's going to come up when you look at the top 30 percent in the Prescription Monitoring Program? Hospice doctors, pain management doctors, pain management nurses. So we decided that these approaches, these blunt instruments are just not the way to go. And establishing a commission within public health departments, within the FDA to look at all stakeholders, and do intelligent regulation is what I would recommend.

Bob Twillman: And one additional thought about this I think is too often, people cast this as an us versus them sort of argument, you know? They've got- We've got folks who are advocating for change to address the addiction and the overdose problem. We got pain management providers. And people see them as opposing sides and I don't think that's really the case. You know, those of us who provide care to people with pain don't want people to be abusing the medications any more than anybody else does. We want to help find solutions. It's not that we object to finding a solution, it's just we object to finding the wrong solution, so evolve this.

Steve Usdin: So one of the other sets of issues I think that we really haven't touched on is treatment for addiction because there's a tremendous amount of stigmatization around addiction. You know, Cindy said that maybe the scope of the problem might be exaggerated. But it's a real problem. What should be done?

Bob Twillman: I think the challenge is for a long time, people have viewed addiction as a moral failure and not as an illness. And I think the number one thing we've got to do is to get ourselves to the place where the culture views this as an illness that needs to be treated as an illness. We're making inroads into that. I think the mere fact that we've got office-based treatment now for addiction with buprenorphine prescribing, the Suboxone, and similar kinds of products is a sign of incremental progress in that direction. But we need to step it up. You know, there was a study that came out recently and I forget the exact number, but it was some shockingly low percentage of people who wanted to get care for substance abuse who were able to get it, because there just isn't availability.

The people who provide that office-based treatment are limited to I think it's 100 patients at any one time. So why not increase the number that they can see? Why not make it possible for them to see 200 or 300 patients for this kind of therapy? Why not make it possible for nurse practitioners and physician assistants to provide that kind of treatment to people? Let's make it much more available so that we can handle the need. You know, again, all we've done for 40 years is focus on the demand the supply side here. Let's focus on the demand side. Let's address this issue by providing an adequate amount of treatment.

Cindy Steinberg: I think we also need better research in understanding who will get addicted to these medications. As Bob alluded to, this is a disease. And I think no matter what it is, whether it's going to be alcohol or whether it's going to be cocaine or heroin when exposed to an addictive substance the disease is likely to manifest itself. And we need to better understand that and get better at finding out who suffers from that disease so we can be sure to intervene before they get into trouble. And hopefully, we'll hear more about that this afternoon. Understanding the genetics and possible biomarkers that would help us understand who's going to do well with these medications, who's going to have problems, and how do we intervene before they even start.

Stuart Kim: And then I think lastly to expand on this education theme is going beyond SEME. We also need to have increased public awareness,

public education through various means- PSA's to help with the issue of how addiction is being perceived.

Bob Twillman: We have to do a better job of training physicians and other prescribers on how to do these kinds of assessments. And, you know, in the alcohol literature, there's this thing called SBIRT, which stands for- I forget Screening Brief Intervention and Referral to Treatment. And it's set up for- intended really for primary care doctors to use this to screen their patients for substance abuse problems to make a brief intervention to get them interested in getting treatment and get them into treatment. We have to train people how to do that kind of an assessment first before we can really get into, you know, what kinds of medication do they really need. I don't think that people are adequately trained to do that. I think it's possible to train them to do that. I think we've got some screening measures that can be used but we also need more providers who really are excellent at doing that kind of in-depth assessment.

I'm a clinical psychologist. And I practiced clinically for 19 years before I took this job. And, you know, the- and I've trained students on how to do this kind of work. But you know to try to find a psychologist who specializes in this area is a real challenge. So we'd you know, not only do we need to train the physicians and other prescribers better, we've got to train the mental health professionals better on how to do this. We've got to make them available to help participate in the screening. You know, this is treating these patients is another case of it takes a village to do so. I mean, you really have to have providers who understand all the aspects of what's going on with people and have them available to be seen and to provide that kind of treatment. So, you know, leaving it all in the physician's lap is a little bit unfair to the physician I think.

In the ideal world and I've just recently learned we don't actually live in an ideal world. But in the ideal world, I'd like to see all the medications be abuse-deterrent or tamper-deterrent. But, you know, given that we don't live in the ideal world and given that it's entirely possible the pharmacy benefit managers are going to say, well, we've got this non-abuse-deterrent generic and we've got this abuse-deterrent or this tamper-deterrent formulation. We're not going to even put that tamper-deterrent formulation on our formulary.

Patients are going to have to pay for it entirely out of pocket. Now you've got, you know, a 75-year old woman who's got chronic osteoarthritis who has to take this medication everyday in order to be able to get out of bed, to move around, to play with her grandkids, and we're going to make her pay out of pocket because somebody else is

abusing this medication? So, you know, I think the question that we struggled with is how do we come up with the position on this issue such that we're taking into account the needs of society, but also the needs of the individual patient. Because in a sense, that position of let's make everything tamper-deterrent is the ideal solution for society.

But it may not be the ideal solution for the individual patient. And so that's why we sort of arrived at this position of saying, "We need to have them available." Somebody needs to say, you know, "I want this for a patient. That patient needs to get it." But for this other patient it's absolutely not necessary, you know? Although granted somebody could steal it from the medicine cabinet. So again, it's only part of the solution.

Steve Usdin: What if you did it the other way around and you said that the default assumption was that it was going to be an abuse or tamper-deterrent drug. And somebody has to make a positive statement that they think that there's a particular patient who's low risk.

Bob Twillman: Well, I think that's- you know, that's something we actually included in the position statement too is that, you know, a physician can certainly write. It's okay to substitute for this patient. You know, God bless them. You know, God bless them, prescribers get a little bit lazy sometimes when they write prescriptions and they tend to write the brand name with the drug instead of the whole chemical name of the entity. And when they do that, what happens is you got the brand name drug. But if you also have something on the prescription that says it's permissible to substitute a generic, then that can be done. And so, I'm fine with that.

Steve Usdin: Stuart, is there some- something that's a practical measure that can help generic manufacturers adopt abuse-deterrent or tamper-resistant technology more broadly?

Stuart Kim: I was discussing before about this regulatory uncertainty and I'll go into a little bit more detail. I think one of the issues that the FDA is facing right now is that they believe these human-abuse liability studies are a good predictor of the likelihood of a tamper-resistant or abuse-deterrent formulation actually doing so when it- once it's been approved and marketed to patients. The difficulty is that the FDA considers these health studies which are expensive to be clinical trials. And under the generic drug regulatory approval process, generic drug companies were not permitted to submit such data to their applications.

That's the conundrum that we're in from a generic drug standpoint is the current FDA guidance is really focusing on branded drugs. And so, again, as a company, you know, we at Mallinckrodt, we want to also pursue incorporating abuse-deterrent, tamper-resistance into our entire portfolio. How do we do that? Well, we're still waiting. And it's a very difficult question and I don't envy the agency's position on how they're going to navigate this. But hopefully, we'll know more by the end of the year as this discussion moves forward.

Steve Usdin: Why don't each of one you take a minute to kind of sum up or recapitulate what you think are kind of the takeaways and what I would say also is what's the low hanging fruit? What are the next steps that drug companies, the Congress, the FDA could take that would actually make a difference.

Stuart Kim: I'll go first. to continue. We need to have these ongoing discussions to build consensus on I think uniform actions. From a manufacturer's standpoint and I see there's a lot of discussion and collaboration between brand and generic companies in the context of opioid REMS. And we all are working to a common goal which is to do the right thing. So, I think it's about collaboration, communication, and partnerships, so.

Bob Twillman: In the context of policy, I would echo a lot of that, you know. We also want to do the right thing for everybody, not just for people with pain but also for people with addictions, and for the few people who have both problems. We want to do the right thing. And, you know, we're out there. We're certainly available. We're happy to talk to people about finding the kinds of solutions that are going to solve the problem without harming people who have illegitimate use for these medications, so call us. You know, invite us to the table. Let us know when you're working on something. We're happy to give comments about that. We're happy to work with getting the right thing done. So, just reach out. We're not adversaries here. We're not saying there's not a problem. There is a problem and we need to address it effectively. But a lot of the broad blunt instrument solutions that are being proposed aren't I'm afraid going to do that.

Cindy Steinberg: I would have two recommendations. One is understand the enormity of the public health problem of pain. I don't think it's been recognized. I think it's a huge cost to our economy and exacts an enormous and unnecessary human toll in terms of suffering. And my second recommendation would be to direct more funds to understanding the basic mechanism of pain in the body. We do not understand pain. We do not understand addiction at the level of the

brain. Neuroscience is making great strides and we need to dramatically accelerate this research.

Steve Usdin: Thanks very much.

Peter Pitts: Steve, panel – thank you very much,

One of the big takeaways from this panel, not that it should be a surprise to anybody in this room but maybe to some of our elected representatives is that this is a complicated problem and there isn't a simple solution that provides CPAN-friendly sound bites.



## **Judy Foreman: The Media And Pain Management**

Peter Pitts: Judy Foreman is a nationally syndicated healthcare columnist, whose columns have appeared regularly in the Boston Globe, The Los Angeles Times, The Dallas Morning News, and other national and international outlets. She also wrote for years to Globe's popular short feature Health Answers. She's a Phi Beta Kappa from Wellesley. And she's, as many of the speakers are today, very personally engaged and passionate about this issue.

Judy Foreman: Thank you. I got into this whole business of pain the hard way. A few years ago. I came down with inexplicable but horrible neck pain. I've been a science writer for my whole career and I'd lie awake at night thinking, what is causing this pain? What is going on? Why would evolution have even created this kind of pain? It wasn't keeping me from putting my hand in the fire. It had no adoptive purpose. And after I finally -- after going to many, many doctors like all other pain patients, finally got some help and I can tell you about that in a minute. I thought there's really a lot here. I am not the only one suffering from pain, so I decided to do a book. It is called "A Nation in Pain: Healing Our Biggest Health Problem". And researching this book has actually been a radicalizing experience for me. I interviewed more than 200 scientists and doctors, and quite a few lawyers, and a number of pain patients, and a few government people, and came away believing that it's outrageous that pain is so misunderstood and mistreated in this country.

Chronic pain is actually a bigger problem than heart disease, diabetes, and cancer combined. It's the leading reason that people go to doctors. And in fact, in 2011, the Institute of Medicine, which is - I'm sure you all know - is an arm of the National Academy of Sciences, came out with a blockbuster report. The IOM is not known as a radical institution, believe me. And this was a blockbuster report. They discovered after a lot of research that there are roughly 100 million American adults, we're not even counting kids, in chronic pain. And this does not include kids as I said, does not include people in the military who have a lot of pain obviously from the various wars we've gotten into, and it doesn't include people in nursing home. So these 100 million is almost certainly a serious underestimate of the chronic pain problem.

And it's estimated by the IOM and the various doctors I talked to that a good 10 percent, as Cindy said 10 million are not just having minor pain that they can more or less cope with, but severe disabling pain. And other people put the figure at about 30 percent.

One of the things that I feel really upset about in terms of the press coverage of the chronic pain epidemic is that the chronic pain problem really is an

epidemic and the drug abuse and overdose problem is questionable whether we call it an epidemic or not. To put in perspective, the government figure shows 16,651 overdose deaths from opioids. And in fact, even the CDC has told me that only 29 percent of those deaths involved opioids alone. So it's a little between a quarter and a third. And yet, opioids get blamed even though people are also taking benzos, benzodiazepines and alcohol. It's opioids that get all the press attention.

And in addition to the agony that pain causes day to day, chronic pain seriously raises the risk of suicide. The risk of suicide for people with chronic pain is twice that of people without pain. So, even though people sometimes say, "Oh, chronic pain that's just a quality of life thing." It's actually can be life-threatening if it goes on for a long time. And no one explains this better than Dr. Elliott Krane.

Video of Elliott Krane:

I'm a pediatrician and an anesthesiologist, so I put children to sleep for a living. And I'm an academic, so I put audiences to sleep for free. But what I actually mostly do is I manage the pain management service at the Packard Children's Hospital up at Stanford in Palo Alto. And it's from the experience from about 20 or 25 years of doing that that I want to bring to you the message this morning, that pain is a disease. Now most of the time, you think of pain as a symptom of a disease, and that's true most of the time. It's the symptom of a tumor or an infection or an inflammation or an operation. But about 10 percent of the time, after the patient has recovered from one of those events, pain persists. It persists for months and oftentimes for years, and when that happens, it is its own disease. And before I tell you about how it is that we think that happens and what we can do about it, I want to show you how it feels for my patients. So imagine, if you will, that I'm stroking your arm with this feather, as I'm stroking my arm right now. Now, I want you to imagine that I'm stroking it with this. Please keep your seat. A very different feeling. Now what does it have to do with chronic pain? Imagine, if you will, these two ideas together. Imagine what your life would be like if I were to stroke it with this feather, but your brain was telling you that this is what you are feeling and that is the experience of my patients with chronic pain.

Judy Foreman: I'm going to interrupt him for a second to say that chronic pain literally changes the brain. It actually decreases the volume of gray matter. There are two colors of things in the brain. The nerve cell bodies, the clumpy part of the neuron is gray and the extensions are covered with myelin, this kind of white fatty stuff that looks white so there's they just call it white matter and gray matter. The gray matter, the cell bodies, you lose 5 to 11 percent of the gray matter in your brain if you have chronic pain for any extended period of time and this is equivalent to 20 years of aging. So you could kind of capsuleize this

as saying chronic pain literally is equivalent to 20 years of aging and this was initially shown in chronic back pain but now through other researchers, it's been shown with irritable bowel and migraine and fibromyalgia and a bunch of other conditions. Anyway, back to Elliott Krane.

Elliott Krane: That was the experience of my patient, Chandler,. She was 16 years old last year when I met her, and she aspired to be a professional dancer. And during the course of one of her dance rehearsals, she fell on her outstretched arm and sprained her wrist. Now you would probably imagine, as she did, that a wrist sprain has a trivial event in a person's life. Wrap it in an Ace bandage, take some ibuprofen for a week or two, and that's the end of the story. But in Chandler's case, that was the beginning of the story. This is what her arm looked like when she came to my clinic about three months after her sprain. You can see that the arm is discolored, purplish in color. It was cadaverically cold to the touch. The muscles were frozen, paralyzed dystonic is how we refers that. The pain had spread from her wrist to her hands, to her fingertips, from her wrist up to her elbow, almost all the way to her shoulder. But the worst part was, not the spontaneous pain that was there 24 hours a day. The worst part was that she had allodynia, the medical term for the phenomenon that I just illustrated with the feather and with the torch. It's successful, as you can see from this video of Chandler, who, two months after we first met her, is now doing a back flip. And I had lunch with her yesterday because she's a college student studying dance at Long Beach here, and she's doing absolutely fantastic. How can the nervous system get this so wrong? How can the nervous system misinterpret an innocent sensation like the touch of a hand and turn it into the malevolent sensation of the touch of the flame? Well, you probably imagine that the nervous system in the body is hardwired like your house. In your house, wires run in the wall, from the light switch to a junction box in the ceiling and from the junction box to the light bulb. And when you turn the switch on, the light goes on. And when you turn the switch off, the light goes off. So people imagine the nervous system is just like that. If you hit your thumb with a hammer, these wires in your arm that, of course, we call nerves transmit the information up to the junction box in the spinal cord where new wires, new nerves, take the information up to the brain where you become consciously aware that your thumb is now hurt. But the situation, of course, in the human body is far more complicated than that. Instead of it being the case that that junction box in the spinal cord is just simply where one nerve communicates with the next nerve by releasing these little brown packets of chemical information called neurotransmitters in a linear one-on-one fashion, in fact, what happens is the neurotransmitters spill out in three dimensions laterally, vertically, up and down in the spinal cord and they start interacting with other adjacent cells. These cells, called glial cells, were once thought to be unimportant structural elements of the spinal cord that did nothing more than hold all the important things together, like the nerves. But it turns out the glial cells have a vital role in the modulation, amplification and, in the case of pain, the distortion of sensory experiences. These glial

cells become activated. Their DNA starts to synthesize new proteins, which spill out and interact with adjacent nerves, and they start releasing their neurotransmitters, and those neurotransmitters spill out and activate adjacent glial cells, and so on and so forth, until what we have is a positive feedback loop. It's almost as if somebody came into your home and rewired your walls so that the next time you turned on the light switch, the toilet flushed three doors down, or your dishwasher went on, or your computer monitor turned off. That's crazy, but that's, in fact, what happens with chronic pain. And that's why pain becomes its own disease.

Judy Foreman: What he said about glial cells, I want to really emphasize. In fact, I have a whole chapter on my book on glial cells. Glial cell is probably a word you've never heard of. They are actually derived from the immune system and so what happens when acute pain turns into chronic pain is called central sensitization. The immune system essentially learns like learning a language. It learns to be more and more responsive to the pain signals, to the point that often, you don't even need the original signal anymore. It becomes its own disease, and what contributes to this is the immune cells, these glial cells. So basically, you have the nervous system working with the immune system, these cells from the immune system to amplify the pain, to crank it up until it gets going like a runaway train and it's really important.

Linda Watkins is probably the country's leading glial cell researcher. She is out in Boulder, Colorado and she was nice enough to let me spend a few days a couple of years ago with her and the reason this is important is, you know, we all know that opioids are a very mixed blessing in terms of drug treatment. If we can really understand how to control the way the immune system kicks in with chronic pain, that gives a whole new slew of potential drug targets. So far, there are no drugs on this on glial cells that are on the market but it really is a very potentially very optimistic thing in the whole pain picture.

In 2011, a group of researchers from Johns Hopkins surveyed 117 American and Canadian Medical Schools basically just trying to find out how much pain education they give to their students. And the answer was pathetic. In their written conclusion in their paper, they said, "Pain education was limited, variable, and often fragmentary." In fact, the median number of hours spent learning about pain, basic pain mechanism, it was nine hours in American medical schools. And yet, remember, this is bigger than cancer, heart disease and diabetes combined. It's the main reason people go to doctors. And yet, medical schools literally do not teach it. In fact, veterinary schools do a better job. The vet students get twice as much pain education on average as medical students. And this is documented by several studies. The one I'm quoting here is from University of Toronto in 2009. So this is -- I mean, I'm all for taking care of pain in animals but we really should be taking care in people. No one is more surprised and just made by this and doctors themselves who inadvertently - obviously inadvertently become pain patients. This is Howard

Heit. He was a gastroenterologist in Bethesda, Maryland. And he was on his way to a meeting at NIH more than 20 years ago and got into a horrific head-on car crash that left him in a wheelchair and chronic pain 24/7. And he was appalled by what he found when he tried to get help for his pain.

I had a long interview with him and he said, "It became apparent to me that my fellow physicians had no idea about pain or how to treat it. If this was being thrown at me as a physician, as a male, what is happening to the average person coming to a doctor?" So having talked to him, I decided to see what was happening to some other doctors.

David Biro. He's a dermatologist in New York City. He had a condition. It wasn't cancer but he needed chemo and radiation. And the radiation caused such severe burns on his scrotum that his skin fell off. And he was appalled that the doctors he was being treated by not only didn't know what to do, but they really they couldn't even emphasize, you would think they could. And he said to me, "We doctors are trained on this medical model. We are not used to going to the next level. What do we do? We say 'Go see somebody else. Go see a shrink.'" Now I happened to like shrinks, I'm married to one and I think they do a lot of good for the world. But this attitude that there's something wrong with your mind that you're causing your pain, that is one of the most insidious and insulting things that happens to pain patients.

Mark Cooper is a pain researcher in Seattle. And he had something probably similar to what I had. His whole body went into spasms and one time his whole body got tipped to the left, and he couldn't pull it back. Every time he tried, it fought back. Eventually, finally, after multiple trips to various doctors, he was diagnosed kind of like I was with a pinched nerve in his neck. But his conclusion was, "If I had been a woman or if I have not had background in neurobiology, I believe that what happened to me might have been viewed as psychogenic pain."

My last example is Karen Binkley. She is an allergist in Toronto. And as you can see she's very athletic. She tripped over the elliptical machine in her living room a few years ago, broke her foot, and the pain didn't go away as it was supposed to as the foot healed. It crept up her leg, her whole leg was discolored, and she had this chronic regional pain syndrome. And like every other pain patient, she had to go from doctor to doctor to doctor even though she was living in a country, Canada that supposedly has really good medical care. Sadly, it is not just medical schools that do a terrible job with pain. The federal government does a terrible, terrible, terrible job with pain.

I was curious how much money the Institute of National Institutes of Health spend on pain research. And it's basically pitiful. I had lunch with this guy, David Bradshaw, who is a pain researcher at the University of Utah. And he took it upon himself to analyze the NIH budget and see how much they

actually spend on pain research. He did this with the 2009 budget but things have actually gotten worse since then. By his calculation, NIH spends less than 1 percent, 0.45 percent of its fairly massive budget on pain research. And again, pain is the leading reason people go to doctors. It's a huge problem. But they don't spend the money. Obviously, as a reporter, I check with NIH thinking, you know, David Bradshaw can't possibly be right. And they gave me a slightly higher figure, 1.3 percent, that has actually gone down in recent years even as the problem increases.

It's hard to fathom how there could be such a colossal mismatch between the need and what the feds spend. Dr. Phil Pizzo is the former Dean of Stanford Medical School. He was the guy who was head of this Institute of Medicine Committee that wrote the blockbuster report. So I asked him, I said, "Well so, you know, how can this be?" And by the way, he did not tell me this but other committee members did. The committee that was looking into pain for the IOM was basically forbidden from asking some of these questions about why the government doesn't spend more in pain. What he would say on the record is, "Because there is no single institute funding pain at NIH, there is not a coordinated allocation, yet, pain cause the nation more than cancer, heart disease, and diabetes combined. The funding for pain research is only a fraction of that allocated for other diseases."

The idea of trying to create an institute for pain or pain-related diseases at NIH is what I would like to see happen, probably will not happen, but it is a disease in its own right and it gets almost no funding from NIH. And if you read my book, there's a bit on what the government is doing. But basically, we have two committees. And last I heard - well, next to last I heard they didn't even have a coffee pot. Their funding is pathetic. So you can imagine how much good these committees are doing. We have in this country what I think of as two colliding epidemics. Only one is really an epidemic. One is the the real epidemic of chronic pain at least 100 million American adults. The other is what's often called an epidemic of drug abuse. But as Cindy said, it's a total mismatch of terminology. The government says there were 16,651 opioid overdoses. This is the last year for which figures are available. Meanwhile, there are 100 million people in pain and 10 percent of them - at least, probably 30 percent are disabled by it. It is true that drug overdoses have been going up but so has the use of medications. And there are something like 200 million prescription opioid prescriptions every year. Most of those people do not abuse these drugs and many are helped by them. In fact, if you look at where if you look at the street abusers and you ask them where they get their drugs, by and large, they're not getting them from pill mills, they are not getting them from unscrupulous doctors. They're getting them from friends and family. If you add up the number, especially at the top, that's about 70 percent get them from friends and relatives.

But the image we have in the press is of this huge criminal element which does exist. But by and large, they're getting them from your medicine cabinet and mine..

So what we end up with is legitimate pain patients who can't get the opioids they need because there's such a fear of them and doctors are so afraid of prescribing them.

An important point I really want to make in terms of the addiction problem is that there is a big difference between addiction and dependence. There are a group of, I guess you could call them antiopioid doctors who say that this is a distinction without a difference. But most of the doctors and researchers I talk to think it is a real difference.

Addiction is a chronic biological disease characterized by impaired controller over drug use, a lot of craving even committing crimes, taking the drugs knowing they're going to you harm. And that is a real primary neurobiological problem. Dependence is very different. People like Cindy and many people I know, many pain patients can take opioids for many years without increasing their doses, without taking the drugs to the point of them doing harm. I mean, it's a very different population. What is true is that if you take opioids for any amount of time, two or three weeks, there's 100 percent chance, a certainty that you will become dependent. That means your body has adapted to these drugs and you need to take them on a regular schedule and a regular responsible way to keep the pain away. And many pain patients do this. And that's very different from the risk of real addiction which is really -- the government says the risk of addiction is between 3 and 25 percent which is a pretty big range. I think that figure is wrong. But even if it were 25 percent, which is obviously huge, that still means that 75 percent of people on taking the drugs would not become addicted. The actual risk is much less. It's probably -- the studies really show the risk of addiction is really close to 3, or 3.27 percent. And if a person has no personal or family history of substance abuse or alcohol abuse, the figure is closer to 1 percent or even below 1 percent. So in truth, many people can take these drugs safely and without getting into problems of addiction.

That said, opioids are not wonder drugs. Overall, they probably only reduce pain 30 to 40 percent. So they're not a slam dunk and even when people are dying in cancer pain. I interviewed one guy at Sloan-Kettering, they were giving him everything under the sun. He was still -- his pain on a scale of 0 to 10 was still an 8 despite all these opioids. They are not wonder drugs.

There're about a dozen genes that researchers are mostly focused on that can ramp up or ramp down a person's susceptibility to pain. In fact, on the basis of a lot of rodent studies and human twin studies, it appears that 40 to 50 percent of a person's susceptibility to pain is inherited and I think this is very

comforting for pain patients to hear because people are blaming themselves a lot and think they're weak and they're wusses or whatever if they have pain.

Pam Costa is a psychologist in the West Coast. She has what they call burning man or burning feet syndrome. She has a mutation in a gene called SCN9A which is a sodium channel gene. Sodium channels are a little like tunnels on the edge of a cell through which these charged particles called ions go in and out and her mutation means that those ions are always going in and they're always turning the nerve cell on. So it's constantly firing 24/7. She has had this from birth and she's in constant pain 24/7 and so were most -- are and were most of the people in her family, in her genetic pedigree. In fact, three of her family members committed suicide because of pain and one was not clear whether it was an accidental overdose or not.

By contrast, there's a girl named Ashlyn Blocker in Georgia. She has a mutation in that same SCN9A gene, but it's the opposite mutation. Instead of ramping up pain, it damps down pain. So she can never feel pain and you might think this would be a good thing, but it's not because she has actually gotten severely burned and broken a couple of bones and nobody could even tell 'cause she wasn't crying. And I was sort of semi-joking with her mother. I said, "Well, at least when she goes into labor, she won't be in pain." And the mother said, "Yeah, but how will she know when to go to the hospital?" Good point.

When girls and boys are born, they have very similar levels of report levels of pain and pain problems but after puberty, the picture changes dramatically and women report a vast disproportionate amount of pain compared to men. And this is not just childbirth that something that could only happen to women. This is like irritable bowel syndrome, migraines, fibromyalgia, things that could affect both, it could and do affect both sexes, predominantly affect women. It's not totally clear why. Hormones probably play a significant role 'cause in general, testosterone protects against pain and estrogen seems to make it worse, except not always.

There was a very interesting study in Italy a few years ago that I don't think has been replicated but it involved transsexuals and when the people went from being male to female, they are taking a lot of testosterone and their chronic pain went down and when it was the other way, female to male when they started taking testosterone, their pain got better. So estrogen in general is a bad actor, except there's a lot of acceptance to that. One of the big problems though is when researchers study basic pain mechanisms, they still use mostly rats, not humans and making matters worse, they mainly use male rats which is doubly ridiculous. In fact, there's a lot of recommendations that researchers at the verily should study female rats and I would --if you have a one take home lesson from today, it go for female rats.

The bigger picture is that if you have chronic pain, you may get depressed because chronic pain ruins your life. It is totally devastating to a person's life. There was a very interesting study that I want to share with you. IT was done by researchers from Harvard and Oxford University in England. They intentionally induced depression in 20 healthy people by having them read statements like "life is terrible", "I'm a loser", and while they were reading these statements, they were listening to this depressing music, which is Prokofiev's "Under the Mongolian Yoke", which was played at half speed. And meanwhile, they're getting stuck by needles and thermal stimulation, and put in a brain scanner.

And in the depressed state which was induced by the experimenters, their pain scores were through the roof. When they did the opposite condition and they had people read more cheerful statements like cherries are red, the sky is blue, life is okay, and they played happier music which in this case is the Dvořák's "New World Symphony". Again, they gave the pain stimulation, had the people in brain scanners. And when they were in a good mood, the pain scores went way down. And this was a very clear demonstration of the interplay between pain and mood.

This talk is basically just an appetizer,. There are many things I don't have time to talk about. There are 100 million Americans in chronic pain. It affects many, many people, 635 billion a year. Medical schools do not teach it, the government barely funds it, and yet to not treat pain can be considered a form of torture.

So I hope you take home from this that pain management really is a fundamental human right. And I have been a journalist for 40 years now and I've watched with awe and respect as people with AIDS and people with disabilities, people with breast cancer, have kind of come out of the closet and shed their isolation and their stigma, and their shame and gone to - busted into scientific meetings and take into the streets and even the halls of Congress to demand that their problems be taken seriously. And I think it's time for pain patients to do the same. Thank you.

### **The Players. The Politics. The Perception.**

Peter Pitts: Let me ask Steve Usdin to come back up to give a talk and one thing I'd like to call your attention to on his bio. In 2012, Steve was presented with the Harvey W. Wiley Lecturer award by the FDA Alumni Association Steve is the first journalist to have received that honor and it should serve to reinforce the seriousness with which he is taken in this community. Steve, thanks for coming back up to the podium.

Steve Usdin: Thanks Peter.

I have been a reporter for over 20 years and for me, it's all about the intersection and in many cases, the collision of medicine and policy -- and describing and figuring out how politics and policy can help or hinder the process of turning science into medicines so that it can help people. And pain treatment is in that intersection.

The really interesting thing to me is that in contrast with a lot of the issues that I report about such as severe forms of metastatic cancer, ALS, Alzheimer's, is that the issues around pain are tractable. They're difficult, they're really tough decisions, tough policy choices. But you can imagine, you can outline things that could be done tomorrow that would make things a lot better for people with pain. And that's really kind of hopeful.

Another thing is the start from first premises. So for me, the premises are that pain is a serious and terrible problem that has to be dealt with. Abuse is a reality and overdoses are realities. There's some you can debate about -- how serious they are, how many people get addicted, how big abuse is a problem, how many people die of overdoses. But, if it's one, it's too many.

The other conviction I have, is is that there are things that can be done, there are policy decisions that can be made, there are scientific research that can be done, there are things that can be done to make all those things better, and the question is how do we go about doing it. One of the contentions that I would have about pain is that there are people in pain and they're somewhere in the city where there's a drug that can help this people, why aren't they getting it. That's true for a lot of people. For a lot of people, there isn't a drug that can help them.

I interviewed Rob Califf, the director of the Duke Translational Medicine Institute for a program recently on another topic. And he said, "We don't know what the safety and efficacy of opioids." What he meant is that they haven't really been studied and that evidence base isn't there.

I did a quick scan and found 170 drugs in development today from pre-clinical to clinical trials that use nonopioid mechanisms of action to treat pain. But there's another track is very interesting -- tweaking opioids to make them work better, to make them more effective as pain therapies, and to reduce the abuse and overdose potential. And there are a number of companies, I'm not going to mention any because I'd leave some out and then they'd get mad at me. But there are a number of companies that are working on really interesting technologies, for example reducing the flow, the rate of which opioids cross the blood brain barrier, there are companies that are working on drugs that when the dose is escalated, it doesn't increase neurotransmitter release and the theory on that is that you can increase you're not going to get

the abuse potential, you're not going to get the kind of high from them that you get from other drugs.

The problem with all of them is that nobody knows what the target is. The target is going to be set by the FDA and it's a tough problem for them to do. But I think, if there are going to be investments there needs to be more investment. There needs to be a much bigger investment in the regulatory science so the companies that are developing these products know what the endpoints are so they know what they have to do to demonstrate abuse deterrence, maybe even to be able to titrate it.

The same with reducing the potential for addiction. If there aren't goal post that they know that they can shoot for and that they can test it in a rigorous way, and then get an approval and put that on the label and mark it as having those characteristics, it's really difficult to see how those drugs could get developed. And if they do, it's hard to see how you're going to convince payers to pay more for them so that they would be used and replaced the other drugs that are in the market today. So I think that that's a critical thing.

I was struck by a comment from the director of the FDA's Division of Anesthesia, Analgesia and Rheumatology Products at an advisory committee meeting that I was at in 2008 and I dug this paragraph up from a story that I wrote then. He said if a company were able to show that its new formulation lower the abuse potential, "We would consider removing other products from the market that do not decrease abuse." And then he says, "We need an appropriate metric to show that there was an improvement and then we'd have to require other companies to change or to create a safer environment."

That's really profound if you think about it. What he was saying is if a company could demonstrate in a rigorous way that they had an opioid or another kind of pain treatment that had less potential for abuse than drugs that are on the market, the FDA would actually take those other drugs off the market. But the kicker is you have to have some way to measure it and you have to have some way to demonstrate it. And I think that that's kind of one of the most important bits of science that could be done to move things forward.

The other thing that I think that is important and that I've noticed and watched in more than 20 years of covering drug development is that there are extraordinary carrots that the government can have, the government has to be able to stimulate certain kinds of drug development.

There are examples, for example, patients and parents of patients who have rare diseases went to Congress a few decades ago and said, you know, "There isn't enough drug development for patients who have rare diseases, and it's a terrible problem." And they proposed that Congress pass a law, and the

Congress did pass a law giving drug companies seven years of marketing exclusivity for drugs for orphan diseases. There was an explosion of drug development for orphan diseases that created -- literally hundreds of diseases got therapies that wouldn't have otherwise.

There are other examples and Congress created a similar kind of incentive. It gave an extension of marketing exclusivity if drug companies did pediatric trials that were FDA requested. That has resulted in labeling that tells doctors how to prescribe drugs for kids. It's been tremendously beneficial. I don't know if those are the right answers here, but I would say that there must be some kind of policy leverage like that that Congress could pull in cooperation with FDA that would create incentives that would mean that a lot more of those 170 nonopioid drugs that are underdevelopment now, actually cross the line and get to people then would otherwise.

I would also mention that I agree with Peter that the DEA is an enormous part of the problem. There's a fundamental lack of alignment. The DEA is a law enforcement agency, they're not equipped and they don't see it as part of their mission to advance medicine. But they are gatekeepers..

One example, there's a company called Eisai. They have an epilepsy drug called Fycompa Eisai got it approved a year ago, but they can't market it until they get DEA scheduling and it's been a year and they haven't gotten DEA scheduling for it yet. They actually sued the DEA a couple of weeks ago.

I don't think that they think that they're going to necessarily win the lawsuit, but it's kind of cry of extreme frustration on their part. And if you understand anything about the economics of drug development, their patent life is seeping away every day. Their FDA exclusivity, the clock on that is ticking and their patience are waiting. This is a drug that's been approved patient -- you know, it must mean because the FDA agrees with the company. This is something that's going to help patients. And it's been a year and they haven't even they don't even know when the scheduling is going to start. The thing that's needed is a -- and there are other examples like this. There are also examples of companies that have a great deal of difficulty providing samples of their products, investigational drugs for clinical trials, again because of problems with the DEA.

It seems to me this is something that Congress could and should look at, you know, should DEA retain this authority, if they should, whoever should have that authority is there a way to put in place transparent regulatory system with timelines on it so that it isn't blocking the progress of medicine.

Peter Pitts:

Thank you Steve.

## **Personalized Medicine and the Future of Pain Management**

Peter Pitts

We've been talking about opioids and treatment of pain, coming from a blockbuster mentality and that's where we've been for the last two or three decades. But we're on the cusp of going beyond that. We're on the cusp of significant advances in diagnostics and companion diagnostics, of being able to actuate the right medication in the right dose at the right time to the right patient, which is my definition of personalized medicine. So let me ask Dr. Charles Inturrisi to come to the podium and let me read you his CV at length because I think it's relevant and extremely impressive.

Chuck is professor of pharmacology at the Weill Cornell Medical College. He also has appointments in the neuroscience program at Weill and with the Pain and Palliative Care Service at Memorial Sloan-Kettering and with the drug abuse center at Rockefeller University.

Chuck's research is measuring the long-term outcomes of treatment for chronic cancer and non-cancer pain received by patients at four hospital-based outpatient pain clinics. So this is real time research, ladies and gentlemen. He's received the John J. Bonica Award of the Eastern Pain Association, a Distinguished Alumnus Award from the University of Connecticut, and the Excellence in Mentoring Award at - again, at Weill Postdoctoral Association. In 2008, he received the first Graduate Dean's Award for excellence in teaching and mentoring of graduate students presented by Weill Cornell Graduate School of Medicine. Again, we talked earlier about the lack of medical schools and of practicing doctors relative to CME. So I think, again, this becomes an extremely important point of conversation, not just kudos deservedly earned. In 2008 to 2010, he was President of the American Pain Society. In 2013, received that organization's Distinguished Service Award. He's a member of the IOM's committee that prepared the 2011 report "Relieving Pain in America". Chuck, come up and tell us about where we need to go from here.

Charles Inturrisi: Thank you. I want to focus on the problem of pain medications, but I want to then move on and talk about personalized medicine. What I'm going to tell you is how you can take what really evolved as a quality control approach in the way events are evaluated in a hospital or clinic environment and turn that into a research tool.

The IOM report gave us a blue print. It gave us a blueprint on what we need to do in the areas of public health, education, treatment and research and I'm going to focus on research, but it really leads very much back to treatment. The question is, how does one begin to build an evidence base for understanding pain medications that are available?

We know about the conundrum of opioids, There's a huge remaining problem of the under treatment of pain and clearly there are issues with what you might call overtreatment of pain, and that we need to strike some kind of a balance. You've heard about this from the CDC. The use of opioid has dramatically increased. I just wanted to add one more factoid to this. As the rate of use has increased, so has the rate of opioid-related abuse, overdose, and death. The CDC reports that in 2012 about third of these involve one single drug called methadone. And, as you also heard, there is substantial evidence that the administration of other central nervous system depressants are major contributors to the problem. So it's not only an opioid problem.

The reason I bring up methadone is it's a very special drug and we've been using it for a very long time. We have a lot of experience with using methadone. It's not a drug that we advocate for primary pain management. There are patients who get wonderful results with methadone, but it requires special education and training.

The problem with methadone is that it has a long and variable half life that makes it difficult to titrate. It interacts with multiple medications and there's variability when switching from another opioid to methadone. And then there's an issue of changes in heart rhythm. All of these issues can be managed if one educates. One additional factoid about methadone is that it's very relatively inexpensive.

A lot of formularies began, in the mid-2000s, to include methadone and in some cases, recommend the use of methadone and this led many problems. But, largely because of physician education programs that have been developed. we've seen in the latest statistics the bending of the curve on methadone overdoses.

Now, I want to make a distinction that really does make a difference. And this is the distinction between efficacy and effectiveness. We know that opioids can provide analgesia for some chronic pain patients. We don't know what percentage, at least some of them. But we also know the treatment outcomes with opioids are variable and not predictable. And this is the take home message if you have to leave. At present, there are no well-validated means of identifying optimal candidates for effective long-term chronic opioid therapy. That's the problem. That's the gap in our knowledge. That's the gap in our evidence base.

We need to learn who will experience good analgesic effectiveness at stable dosages with limited side effects and low risk of abuse. So the critical question there is are there phenotypic or genotypic characteristics that we can associate with better or worse outcomes that will help us to predict which patients might benefit and so that the cost-benefit ratio will be favorable rather than unfavorable.

Now I'm going to talk about personalized medicine in general and then in particular. This refers to this emerging concept approach that uses patient-related factors including the phenotype, i.e. what information you can observe about the patient and a lot of that information now is contained in the electronic medical record. Also genotypic information that you can gain by collecting a sample and it can be either a sample of blood, or in some cases even a sample of buccal cells from the mouth and by going through and looking at SNPs of DNA and identifying biomarkers that are predictive of optimum medication and dosage for individual patients.

It's been estimated, on average, that prescription drugs are effective for only about half of those who take them. And for some drugs like anticancer drugs and antidepressants, the so-called non-responder rate is even higher. Personalized medicine can reduce the non-responder rate because you can focus in on individuals who are highly associated with being responders and you can eliminate the trial and error inefficiencies that inflate healthcare cost.

You've already heard about this concept of treating patients with one drug and then converting to another drug and another drug and trying to find the right combination. So, for example, we know that for neuropathic pain, tricyclic antidepressants that have analgesic properties work in about a third of the patients. But we don't know enough about the characteristics of patients in which these drugs are going to be effective that we can just select that one third of patients. So you can see two thirds of patients are getting a medication that's not going to provide them with much pain relief. Personalized medicine could reduce or eliminate that and therefore it could also influence the way new drugs are developed, impacting the time, cost, and failure rate of pharmaceutical clinical trials.

Analgesic trials are failing at a rate that's absolutely astounding these days. And there are a variety of factors that go into this, but it tends to discourage the pharmaceutical industry from becoming involved with analgesic clinical trials with drug development associated with analgesic, even though there is a huge problem. Personalized medicine is being used. It's currently being used to predict responses and dosing of patients undergoing treatment for breast cancer. Can we develop an evidence base for personalized medicine for the management of chronic pain with opioids? Part of the problem, is the randomized controls trials used to get drugs approved and on the market. They're the gold standard for demonstrating analgesic efficacy.

Remember that term I told you about? Now I'm going to separate efficacy from effectiveness. Clinical trials are optimized to demonstrate efficacy, that is the mean analgesic response in an active treatment versus placebo condition. So the idea is you want to show that a group of patients with a condition under treatment are going to respond better to your drug than they

are to the placebo. However, for a number of reasons, e.g. the way populations are selected, a lot of patient characteristics that are associated with what I call real world patients are excluded. So if patients are too old or too young, if they have a history of drug abuse, if they have a lot of comorbidities, they tend to be excluded from many of these randomized controlled trials, and because of the cost and the FDA requirements, these trials are of relatively short duration.

If Dr. Throckmorton were here, he would say the following, “We have good data on opioid efficacy for 12 weeks.” There’s good data on that. We don’t have good data going beyond that, and that’s part of the big conundrum. So I’m going to discuss -- the clinical question that we really want to answer, who among real world patients will have the best long-term outcomes? Effectiveness is what we really want to know once we’ve established efficacy. So who is this drug going to actually be effective for? Does it make a difference if you have renal disease, if you have depression, if you also have diabetes or heart disease along with your pain? That is important and that information- is not -available from the usual randomized controlled trial. Sometimes there’re secondary outcomes, but often they are not very useful.

I’m going to discuss the use of a concept called a Registry that observes characteristics, treatments and outcomes of real world chronic pain patients as one method. It’s not the only method of gathering information that can be used to create this kind of evidence based personalized prescribing of opioid analgesics for those patients likely to benefit from treatment. So what we’re doing is looking at a quality improvement approach. The IOM report and an NIH expert panel identified many of the knowledge gaps that we’re talking about here, and said that they could be addressed, at least in part by increased support for longitudinal research in pain including comparative effecters.

We have a real world experiment,. Patients come to pain clinics and they’re treated with standard treatments and then they’re followed for long periods of time. A lot of the information about them is available in the electronic medical record. As Stuart Kim said, we need more information about outcomes. I’ll show you how we’ve incorporated measures of outcomes into our approach so that we can have not only the patient characteristic information but also the outcomes. So we use something called Practice-Based Evidence, it was developed by my collaborator, Susan Horn. It’s a prospective observational method for determining which treatments and patient characteristics are associated with better or worse outcomes. Susan has used this approach with many different treatments including diabetic treatments and wound-healing treatments.

Susan had never gotten into the pain field before. So my good fortune was to be able to convince her that we should try this with pain patients. So we’re going to measure effectiveness. Which patients does it work? We’re not

measuring whether or not it works, but in the course of that we're going to find out a little bit about efficacy. So what can we do? We hope that we can identify subpopulations of chronic pain patients that benefit from certain pain management treatments. I can tell you we've already done that, and I'll show you briefly -- I am an academic, I need to show you a little bit of data of combinations of treatments, drug and non-drug that provides superior relief. As everyone before me has said, we need to use combination approaches. Combination approaches are standard treatments in many certainly in the pain clinics that we're involved with. And so - and these are extremely hard to measure with randomized controlled trials because you need control groups for each of the treatments, but they can be observed and evaluated in the kind of registry model.

We obviously can also measure adverse effects or harms associated with long-term therapy including if we measure the right outcomes, aberrant drug behaviors, misuse, even diversion of opioids. And then we can ask important questions about patient and clinic reasons for discontinuing pain management therapy or for beginning another treatment. So there are a lot of data out there showing that patients take a drug, an opioid or a nonopioid for a certain period of time and then they switch to something else. But we have no idea whether the reason they switched was due to adverse effects, failure of the treatment to produce analgesia or some combination of it or whether when they switch to something, they got any better. So it's important to be able to follow all of these things if you're going to properly evaluate.

We put together what's called the Tri-Institutional Chronic Pain Registry. There are three in New York City institutions. I don't know if you know but on the corner of York and 68th Street. If you stretch in any direction, you will come in contact with one of these institutions. They are Weill Cornell and the New York Presbyterian Hospital and The Memorial Sloan-Kettering cancer center and the Hospital for Special Surgery. patients who come to these pain clinics back and neuropathic pain at Weill Cornell. At Memorial Sloan-Kettering are cancer patients but I must tell you, there's been a change in the landscape in the last 5 or 10 years in that about 20 to 25 percent of the patients that are seen at the two pain clinics at Memorial are patients who have chronic pain as a result often of their treatments, (radiation and/or chemotherapy) or their disease or some combination but they don't have a diagnosis of active cancer, so that there is a subpopulation of cancer patients who begin to look more like chronic noncancer pain patients because of their survival, and then the patients at Special Surgery are orthopedic patients. So we have a wide spectrum of pain conditions.

We are also collaborating with the Department of Public Health because we want to be able to look at some of the cost factors involved in this. And so we can make some effort to determine the cost effectiveness of the various treatments. We make participation standard of care so that every patient who

comes to the clinic who has a diagnosis of chronic pain is in the registry and we don't exclude anyone. Patients can refuse to take a survey, most do not, 90 to 95 percent of them are happy to comply. During the last year and a half, we entered about 2800 patients in the registry. Elderly patients make up about a third of our patients, almost 40 percent are 65 and older, but we have a wide range of ages in the registry. And there's a lot of information about how the registry was put together in this article on the slide.

So what are we collecting? We can collect, as I said a lot of information from the electronic medical record, so we need to know a lot about medications, current and past, All of the interventions and procedures that patients receive are tracked by the billing system. So we can cross-reference the electronic medical record with the billing system and we have verified that indeed these are the procedures that patients are receiving.

We have devised surveys for complementary and alternative medicine because about 50 percent of our cancer patients are taking CAM therapies along with their regular treatments based on the survey that was done a few years ago, a number of them getting cognitive behavioral therapy and physical therapy. We believe these are important adjuncts and we need to know particularly with respect to pain whether patients feel that these treatments are helping them with their pain. . There are about 300 pain codes that we had to get together with all of the clinicians from all of the four sites and put this information together along with all of the other diagnostic codes so we know everything about demographics, medical, surgical, and social histories. All of this of course is coded information so we don't have patient names associated so we've maintained confidentiality.

Susan Horn has developed the comprehensive severity index. We use it to stratify patients by severity of their illness. Diagnostic codes are a variable that you need to control for. An example might be a patient who's a terminal cancer patient at Memorial who has the same diagnostic code for pain condition as someone at Special Surgery who playing golf every weekend. So clearly, they don't have the same severity of illness so we need to stratify for that. These are all standardized validated outcomes that are, recognized by the FDA, the CMSAS was developed at Memorial years ago and it measures physical and psychological distress Aberrant behaviors are measured the Current Opioid Misuse Measure. It's used in about 1,000 pain clinics around the country. The point here is that we don't believe that pain is evaluated or treated on the basis of a pain score alone. If your pain score changes but your psychological and physical distress doesn't change, then we haven't done very much for you.

We want to be able to use all of this information to measure outcomes and then we can do a cost analyses. So how would you do this these days? Well, we've made these outcomes available on an iPad which you can you give to

patients in the clinic. While waiting they can fill out the survey information using the iPad. We tested this with a small group of patients and we found it takes no more than 10 to 12 minutes to fill out the survey. There are 34 items in the survey. It goes very quickly. There's a body image that lights up so it verifies where the pain is and this is important because often, many of the diagnostic codes provided by the clinician code for extremity pain. Well, we want to know where the extremity is located and so the patients tell us where their pain is located. In addition, we can watch over time to see whether the pain migrates or not to different areas.

On the next slide is information that the clinicians asked us for and I know you can't read all of the detail. But this is a summary that's generated at the clinic visit. As soon as the patient finishes filling out their iPad survey, we are able to generate what we call the clinicians report and what this is, is the treating clinicians are provided with a one-page report that includes the response to the current visit that they just filled out and the previous visit so that significant changes are bolder and there's an explanation and there's an area for patient comments. Then the dialogue can go something like this, "I see your pain has gotten better or worse but now you're having more side effects so let's talk about a treatment paradigm that will address your problems."

It's virtually impossible to cover all of these questions in a standardized interview. But here, we're actually beginning with the information on hand plus all of our clinicians have access to this information. So if they want to look up the patient's outcome reports for the last year, they can simply go online or they can ask me for a copy. Surveys are successful when patients believe that their responses are considered in their treatment. And one of the comments that we often get here is, "This is the first time I've ever filled out a survey that actually has something to do with my treatment."

You know, you go to the doctor, you fill out a survey and it disappears into cyberspace and you never hear anything about it again. Well, this one is actually part of the treatment paradigm and as I say, clinicians can engage the patient by using this to begin with. So just a little bit of data. First of all, we wanted to know the levels of pain across the three pain clinics because we have very different kinds of pain and at least in terms of diagnosis with cancer pain versus orthopedic pain versus a lot of back and neuropathic pain. So we stratified patients by whether they had reported that their average pain was mild pain, moderate pain or severe pain. And the first thing we found is that not everybody has severe pain, so some of the patients in the clinic presumably are benefiting from some of the treatments that we're providing and you can see across the board and this was interesting 'cause we didn't predict this.

About a third of the patients are showing that on average in the last 24 hours before their clinic visit, they report their average pain as being mild, but another third moderate and above 40 percent severe pain and we can look into these in other ways that I won't go in to now. The important thing is that across the three pain clinic sites, pain intensity is strongly correlated with interference with activities of daily living so that their ability to work, their ability to sleep, to engage in activities with their family, all of these are part of the survey. And these are well correlated with an increase in the pain scores. So as their pain gets worse, interference with activities of daily living gets greater and as average pain intensity increase, there's a corresponding decrease in the self-report of health status.

Our patients do have a lot of physical and psychological distress as Judy Foreman referred to and so therefore, we can show at least indirectly that a lower pain score is associated with a change in physical and psychological distress. Now we've begun a patient level analysis to determine what patient characteristics might be associated with being in one of those categories.

We've initiated a project to provide us with patient experiences and preferences. We just don't want to know what happen to the patients and what their outcomes are, we want to know what the patients think about this experience of having their pain managed poorly or well. So we'll be better prepared to explain their treatment options, the benefits and harms of those options, and importantly, what individual patients can do themselves to improve their outcomes because while our patients are in a pain clinic, the IOM report found that about 50 percent of those 100 million projected patients are self-treating their pain. So we need to know more about what we can tell individual patients to improve their outcomes.

In addition to looking at changes in DNA sequences that are associated with pain or pain prevalence, we can also look at metabolic profile. If you think about it, when you take a drug, the drug is metabolized in the body and it's eliminated - it's in the bloodstream and it's eliminated in the urine. And if you think about it, you can create a kind of signature of that metabolic profile. How much of the parent drug and how much of the various metabolites? And if you don't metabolize the drug because of you're missing an enzyme, then you have a very different profile. And whether or not that profile might be associated with a better or worse outcome is another way to think about it. So you can think about it at a genetic level and then the sort of operational level is what happens in terms of metabolic profile. We can do both of these.

The problem with these studies is that the applications and significance have been limited by relatively small sample sizes. If you think that there could be many, many changes in a genomic sequence that could lead to differences, often, you end up with very small subpopulations. Well, we have bigger populations. We have 2,800 patients across the three sites. And we can

divide those into rather specific phenotypes so that we can engage more than a few patients in this kind of an analysis.

Our study will apply genomic and comprehensive metabolic profile to small molecules and what we call well-defined chronic pain patients phenotypes. We can begin to look at patients who did well on certain treatments or combinations of treatments and patients who didn't do so well -- and see if we can identify any kind of a biomarker. These would then lead to the identification of a biomarker that's often a metabolomic profile -- a molecular signature. In the case of genomics, it may be a particular protein.

We have the capacity at Cornell to do both whole genomic sequencing, informatics and metabolomic profiling. We think that what we're doing will promote personalized medicine, improve analgesic research because we think that we can not only improve effectiveness at the clinical level but information that we learn about biomarkers might be very useful in preclinical analgesic development. We know that we could improve the outcome of efficacy studies if we had better idea of what patients are likely to provide us with an efficacious outcome to a particular treatment.

Peter Pitts: Thank you Chuck.

**PANEL DISCUSSION: Peter Pitts, Steve Usdin, Judy Foreman, Charles Inturrisi.**

Peter Pitts: Steve, I want to ask you a question. You spoke to some people inside the industry. Did you feel there was a red thread, any type of common agreement as to a common front that industry can take to move this whole debate forward?

Steve Usdin: No. First of all, when you say *industry*, people have very competing economic and intellectual interests. I spoke with some companies that are developing abuse-deterrent or tamper-resistant technologies and they had certain approaches that they recommended. Then there were companies that are developing either new forms of opioids or other kinds of drugs --and they're very skeptical about the value of abuse or tamper-resistant drugs and they basically say that's not a useful track to go down. And then you've got the generic companies that have other concerns about the extent to which abuse or tamper-resistant technology can be applied to generics. So they're coming from different places and I don't really see how you could combine them all, except they all have this common need for standards, for FDA to have standards, and for the science to be developed around standards of what abuse-deterrence, resisting overdose potential, and some of these other metrics so that they could they can test for them and get drugs approved for them.

Charles Inturrisi: I think, we have something that they're all interested in. I think the registry concept could be appealing to more than one pharmaceutical company even though they are competing, at the same time. One of the reasons being that the

FDA is pressing them. For some of the issues like the long-term effectiveness of opioids, and their safety, I don't think we're ever going to get an RCT that's going to be able to provide these data.. But it may be important to get some clarification somewhere about whether or not the FDA thinks the registry is useful. I know the FDA is very interested in opioid conversion ratios.

Peter Pitts: If the FDA says on a class-wide level, "we want a registry. And we want, to see adverse event issues coming in to this registry. And we want to capture, real time outcomes issues." What about the financial burden for putting that theory into practice for all intents and purposes comes back down to the manufacturer. And I guess my question is that a worthwhile expense? Is that something that a manufacture should embrace?

Charles Inturrisi: It's in the interest of FDA to say "If you're going to do this, this is *how* you should do it.",

Peter Pitts: So from the FDA's perspective kind of thinking outside the RCT box.

Charles Inturrisi: Yes.

Peter Pitts: Judy, when you talk to a consumer audience, I would suspect that the kind of the visceral reaction is "Oh, my God. How could this possibly be happening?" What does an audience of non-clinicians, of non-policy wonks feel is the key to solving this problem? Or the key to abstracting the solution to the problem?

Judy Foreman: Well, I think there's a lot of anger at doctors for not fixing the problem. A lot of people go to six or seven doctors and they just get enormously frustrated. So they kind of blame the person that they see, who's the doctor. They don't see the big infrastructure picture. I don't think, you know, if I say, "Gee, you know, doctors don't learn about that in medical school," and they all say, "Yeah, yeah, they really don't, they should." But that's where it stops. They don't see the big policies issues of the government in medical school. So they just want help for their problem soon.

Peter Pitts: Chuck, is there an opportunity, you were talking a lot about education earlier relative to patient registries, to more directly engage the patient in patient registers?

Charles Inturrisi: Absolutely. Patients really feel that they have a commitment to this because they see there's an immediate feedback. The information is part of the discussion of their treatment. And their self-report has meaning to the clinician. You know, I think the reason for that is that the people we are involved with are committed. I know some wonderful things are being done with imaging, but we don't have that capacity yet, so that the patients self-

report of pain and their circumstances, are still important.. So if somebody says, "I have a pain of 10. But, you know, I played 36 holes of golf on Saturday and I work seven days a week." So, you know, that pain score doesn't have much meaning. But if that pain score means that you have a lot of physical and psychological distress that you're thinking about suicide. These are important issues that need to be discussed with the clinician. The easier you can make it for the patient to convey that information to the clinician and that - that information has real value because we value it, the patient values it certainly and the clinicians value it, I think that's very important.

Peter Pitts: Steve, how does how does this type of thinking impact how you can label a product?

Steve Usdin: I think that the key is that you have to have some kind of objective standards and the kind of registry data that you're talking about can help in generating that. But if there isn't a goal post that you know that you're trying to hit, then it gets to be, you know, very fuzzy. And it comes up in these discussions of products for abuse-deterrence. How much abuse-deterrence every can have -- you replay the same conversation over and over again when you talk about that and say, "Yeah, there are kitchen chemists who can get around anything, so does that mean that the whole thing is useless and it comes back to you. No, it's not useless because not everybody is kitchen chemist, not everybody is going to do that. But you have to be able to have some way of measuring this, some of kind of goal post.

Peter Pitts: Chuck, what about molecular diagnostics?

Charles Inturrisi: We're certainly in that era and we have seen the beginnings of it in the pain field. So we want identify patients who have something that we all agree is a phenotype. Now, we haven't established them all yet. But we want to get patients who have these and we want to see if there are genetic or metabolomic differences that distinguish these patients. . It's a costly study. But nevertheless, when you're finished, it's likely that you're going to come up with something because you really started out with the sort of classical two-cohort approach rather than just saying, "Well, I know that there must be something out there so we'll just screen hundreds and hundreds of genes and try to figure out what the outcomes were that we wanted.

You know, for example, we've been in - we've been discussing this with at least one company and they were collecting samples as part of an RCT. And they thought it was a great idea that we sort through both sets of samples and look at their RCT samples where they had very specified endpoints. And then maybe look at our patients our real world patients and see if we can get any information that might cross-tab together.

You have to be forward thinking, you have to be willing to take a chance, and you have to make the assumption that you may end up with something that maybe the FDA doesn't like at first.

Peter Pitts: Three things that stick to my mind from today's conversation. I'll call them the three Gs. You have *guidelines* that come from a restrictive perspective, good or not good. Next are *goal-posts*. And third are *genotypes*. Steve, to your point about a more 21st century view towards drug regulation and genotypes. And Chuck, to your point, as to where do these really all need to go in the short term relative to outcomes and the longer term, relative to more sophisticated diagnostic tools.

Panel, ladies and gentlemen, thank you so much for coming.

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