What are the most pressing challenges–and exciting developments–in pain research?

In conversation with...Nathaniel Katz, MD, MS

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Dr. Opler: Dr. Katz, could you tell us a bit about how you got into the field, what your research focus is and why it matters to you personally?

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Dr. Katz: I first trained as a neurologist in Boston. It soon became obvious to me that our clinics were filled with patients with chronic pain. I felt that I needed to get more training in that area, so I did a pain management fellowship, also in Boston, and then spent my clinical career at Brigham Women's Hospital and managing the pain program at the Dana Farber Cancer Institute.

My research focus has evolved over the last 25 years. Initially, my main interest was the opioids–both their benefits and their harms, since understanding them has been an important issue for literally thousands of years. I saw an opportunity to shed more light on those areas.

In the past 10–15 years, I began to grow more interested in developing new treatments for pain, and I discovered how difficult the processes of clinical trials can be. As a result, my primary focus has been trying to figure out what can go wrong in clinical trials and how we can make them better.

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Dr. Opler: What do you see as the top three challenges in current trial methodologies and trial conduct?

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Dr. Katz: Well, it's a challenge to narrow it down to three. Whether the patients are reporting their symptoms accurately would be number one. The second is the placebo response. The third is patient adherence to medications. I'll expand on each of those.

In terms of accuracy in symptom reporting, when I got interested in clinical trials the assumption was that as long as you gave the subject

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***Dr. Katz**, Chief Science Officer and the founder of Analgesic Solutions, shared his insights during a recent conversation with Mark Opler, MD, PhD, chief research officer at WCG's MedAvante-ProPhase. WCG recently acquired Analgesic Solutions.*

The interview has been edited for clarity and length.

a validated questionnaire, everything would work out fine. We questioned that assumption, and our research, based on multiple clinical trials, showed that patients vary quite a bit in how accurately they report their pain.

We have every reason to believe that applies across the board to any other subjective symptom as well–and that you can quantify how accurately somebody reports their pain. You can then use that as a tool to screen out people who can't report pain accurately; there's no reason to expose them to risks if they can't provide useful information.

We've also shown you can train patients to report their pain more accurately; the results of that has been an accurate pain reporting training program that has been widely adopted throughout the industry. Even more important than that, however, is shattering the dogma that we can just ignore the role of the individual in generating accurate research results. Instead, we can do better by supporting them in reporting their symptoms accurately.

Number two–everyone's familiar with the specter of the placebo response, and we've done a lot of work trying to figure that out. It turns out that the cause has surprising and unexpected links to the first problem, accurate pain reporting. By getting patients to be more introspective about what's going on inside their own bodies, you can also train them not only to report their pain more accurately but, in some sense, inoculate them against the external cues that drive the placebo response.

As for the third–there are so many challenges, but patient adherence has got to be very high on the list. We know that medications don't work if the patients don't take them. Contrary to widespread belief, adherence to pain treatments is poor, measurement of how much study drug patients take are woefully inaccurate; there are also failed trials that were positive in the compliant subgroup. It's shocking how little we do in clinical trials to address that issue.

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Dr. Opler: What advice do you have for those planning clinical trials in pain–related areas?

Dr. Katz: I think the most important overall consideration is this: When your protocol is done, before you hand it off to your operations group for execution, take a good, hard look at it. Ask yourself, what you are actually asking people to do? Where might people's performance vary, one investigator to another, one patient to another, one study coordinator to another, etc.? And in those different areas of performance, identify which would have a major impact on the primary endpoint.

Based on that, implement a comprehensive plan to provide either training or job aids or surveillance or enhanced monitoring or other techniques to support these activities. That will help ensure that people are hitting performance targets in terms of how well they perform their roles in your clinical trial.

We do that in a formal way, called a "Data Quality Risk Assessment." Once completed, it suggests various specific

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actions to take. There's a whole list of things people need to do to help research participants achieve performance specifications. Mapping that all out up front may lead to changes in the protocol, but it will help support a creation of different methods to promote performance across all aspects of the study.

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Dr. Opler: Tell us about a couple of the clinical research developments in the past year or so that excited you?

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Dr. Katz: New molecular entities have not done well in pain research over the last quarter century or so. Very few pain products address new targets that would supplant the very limited treatments available today. In the last year or two, however, we have seen some signs of a reversal of that trend.

For example, we have the anti–nerve growth factor antibodies that are in development in two very large programs. If those end up getting approved, that will be, I think, the first major new molecular entity for pain to have entered the pain market in a long time.

We've also had successful approvals of anti–CGRP antibodies for migraine. That's another area where it's been a long time since a new molecular entity has hit the market. There are other exciting products in development, new molecular entities that are breaking the mold of lackluster performance we've had for such a long time.

These are exciting to me for two reasons. The first is the obvious: Patients will now have more treatment options--options that are not just reformulations but truly new therapies. This is not to say that reformulations can't improve over existing products, it's just that any improvement with reformulations is incremental, rather than breakthrough.

A second reason is more subtle, but it ultimately may prove even more important. We can use these examples to start thinking about what went right in these programs and how that contrasts with what has gone wrong in other programs. So we can start to learn broader lessons about developing analgesic drugs that may help energize a whole generation of programs to come.

I think the major learning that will arise from comparing the success of some of the current programs to past failures is this: A focus on methodological rigor is what makes the difference between a successful program and a failed program.

And that's being pursued, I think successfully, although with fits and starts as well, in two arenas. There's been a tremendous focus to try to examine where clinical research methodology needs to be improved so we can actually know whether our treatments are working or not.

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In parallel, on the basic science side, there's been–for the first time in a generation–the beginnings of an honest self–examination where basic science research methodology has led to non-reproducible results and to failures in the clinic. I think those two areas of honest self–examination, on the clinical and the basic science sides, will make a difference for the next generation of drugs and development.

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Dr. Opler: What do you see as the top three opportunities for clinical development in pain and analgesia?

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Dr. Katz: In terms of clinical research methodology, I think over the next year we will start to see the emergence of approaches to promoting comprehensive best practices in clinical trial design and conduct. Over the last 15 or 18 years, especially in pain, we've focused on improving clinic research methods in a piecemeal way. First, we have a paper on what's the best measure, then we have a paper on what are the best domains, and then we have a paper on how to develop new measures, etc.–it's been rather fragmented.

But over the next year or so, we will see syntheses emerge where we have comprehensive sets of best practices that cover not only a few areas, but everything together, like adherence and concomitant medications and controlling physical activity and the whole long list of things that have to be taken care of in order for a trial to generate an accurate measure of the effectiveness of the treatment being studied. And I think that will usher in a new area of clinical research.

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Dr. Opler: That would be a very exciting development and a nice model for other therapeutic areas as well. I have one last question: What do you see coming down the road over the next nine to twelve months?

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Dr. Katz: The pendulum of energy and resources expended in the development of treatments for pain has swung back and forth over the last century, since the 1920s when the federal government, in response to the first prescription opioid crisis after the Civil War, initiated a program to try to find better treatments for pain. That lasted through most of the 20th century, but towards its end– maybe the last 15 years or so–enthusiasm waned and the government funding for pain research became virtually zero. Investors started leaving the pain space because of all the failures I alluded to earlier.

However, a few hardy souls stuck it out, and some courageous companies have continued to invest substantial amounts of resources. Also, in response to the current opioid crisis, the federal government has recently pumped almost a billion dollars into pain and addiction research.

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I also think a few of the programs I mentioned earlier will read out. Some have been approved already. I think the combination of governmental investment into research and the success of some pharmaceutical companies in getting new molecular entities over the finish line–as well as what I hope will be translation of FDA comments about accelerating the development of analgesics into actual FDA practice–will get investors interested again. I think the pendulum is going to swing very forcefully in the direction of renewed investment in pain research over the coming decades.

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Dr. Opler: All of which can only be good news for patients and their families who suffer with pain conditions, so good to hear. Any final thoughts?

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Dr. Katz: Maybe only one, which is that we've learned a lot by very close examination of what can go wrong in pain studies and figuring out how to remedy those problems. The same principles apply in any therapeutic area. Now what I'm hoping is that, as we come to shine a light on how to do better quality pain research, we can at the same time try to work with others, such as yourself, in adjacent fields, to carry those principles into other therapeutic areas that can benefit from similar approaches. We're looking forward to those collaborations in the coming years.

Interviewee

Dr. Nathaniel Katz is considered one of the leading experts of treatment and clinical study design in pain clinical trials. He is a neurologist and pain management specialist with a distinguished career at Harvard Medical School, Brigham & Women's Hospital and Dana Farber Cancer Institute. From 2000-2004 he served as Chair of the Advisory Committee, Anesthesia, Critical Care, and Addiction Products Division, United States FDA, during which time he completed a Master of Science in Biostatistics at Columbia University.

Dr. Katz founded Analgesic Solutions with the mission of modernizing the design and conduct of pain clinical trials to advance the "scientific quality" of pain clinical research, and empower effective treatments for patients. He is the Principal Consultant in charge of scientific oversight at Analgesic Solutions.

Dr. Katz's holds the position of Adjunct Associate Professor of Anesthesia at Tufts School of Medicine. He has completed numerous clinical trials of treatments for pain, both industry-initiated and investigator-initiated, involving pharmaceuticals, non-pharmaceutical analgesics and devices, and has also conducted studies related to opioids, pain, addiction, and other issues related to opioid therapy. Dr. Katz was an Associate Editor at the Clinical Journal of Pain, and Associate Editor (Pain) for the Encyclopedia of Neurological Sciences.

Interviewer

Dr. Opler joined WCG in 2017 as Chief Research Officer at MedAvante-ProPhase. In this role, he directs scientific research and development and leads ongoing studies in psychiatry, neurodevelopment, and other areas of neuroscience.

In addition, Dr. Opler is a faculty member in the Department of Psychiatry at New York University. His academic research focuses on the etiology, phenomenology, and treatment of serious and persistent mental disorders. He is a co-author and developer of several clinical assessment tools, including the SNAPSI, CGI-DS, and NY-AACENT. He is also a contributor to the latest edition of the PANSS Manual©.

Dr. Opler has received research support from the US NIMH, the Brain & Behavior Foundation (formerly NARSAD), the Stanley Medical Research Institute, and the Qatar National Research Fund. He has co-authored more than 50 peer-reviewed publications and has contributed to multiple book chapters and review articles on clinical assessment, research methodology, and mental health.

He received his PhD and MPH from Columbia University and his BSc from SUNY at Stony Brook. He is a graduate of the Psychiatric Epidemiology Training Program at Columbia University and completed his postdoctoral fellowship at the New York State Psychiatric Institute.