Accelerating the Development of Improved Pain Treatments: ASA and the ACTION Public-Private Partnership

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Despite the advances that have occurred in medical treatments over the past several decades, the development of novel analgesic medications has lagged. At present, the only analgesics that are used widely are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, all of which have serious, potentially life-threatening toxicities, even when used properly. Although there has been increasing attention within academia and the pharmaceutical industry to the development of novel analgesics with improved efficacy and safety, demonstrating the efficacy of these drugs in clinical trials has proved challenging. It is possible that the designs and methods used in clinical trials have contributed to disappointing results and that improvements will yield more successful results. This hypothesis is certainly supported by the frequent failures of clinical trials of opioids, given their generally well-established efficacy across multiple acute and chronic pain conditions.

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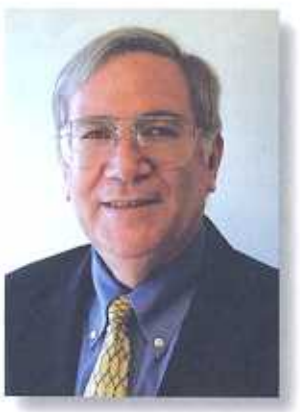
Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA), and her colleagues noted that a public-private partnership for pain "may be the catalyst that is needed to enhance translation of scientific opportunities into improved pain relief for chronic diseases and their associated symptoms."[1] Emphasizing the need to improve the development process for analgesic medications, Dr. Woodcock subsequently noted that research into better designs for pain trials might identify "highly effective drugs with more easily managed risks."[2] This scenario could occur by increasing assay sensitivity or study efficiency, thereby making it possible for treatments with novel mechanisms of action to be made available to the public more rapidly.

Further emphasizing the need for safer and more efficacious pain treatments, Margaret Hamburg, M.D., Commissioner of the FDA, recently announced a "Regulatory Science Initiative" in which the development of improved analgesic medications was highlighted, and it was argued that: "We are facing a global epidemic of prescription pain medicine abuse and misuse. At the same time, patients in agonizing pain are often left untreated. New pain pathways have been discovered and new medicines are being developed that can help. But to accelerate the delivery of new treatments to patients, we need to find better pain models, measurement tools (including patient-reported assessments) and clinical trial designs to enable development of effective medications with less potential for abuse."[3]

On the basis of these considerations, the FDA recently launched the Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) initiative, which



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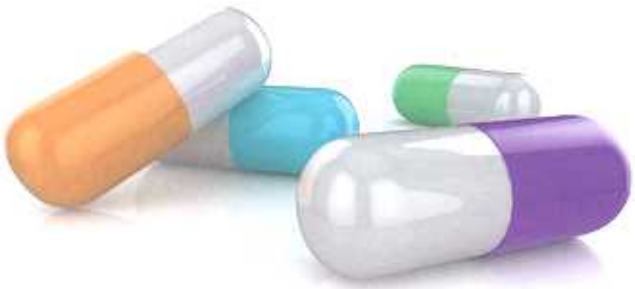
will conduct a wide range of methodologically-focused studies of clinical trials of treatments for acute and chronic pain. ACTION also will also undertake other projects and activities intended to improve the efficiency of analgesic clinical trials. The objective of these efforts is to identify problems and challenges in clinical trial design and implementation and to find ways to bridge these gaps to speed the development of improved pain treatments.

To provide the infrastructure and scientific coordination for ACTION, the University of Rochester was awarded a $1 million contract last September. This contract provided the basis for establishing a public-private partnership in which national and international public and private organizations – including professional societies, patient advocacy groups, industry and government agencies – have begun collaborating on multiple activities designed to accomplish the objectives of the ACTION initiative.



Denham S. Ward, M.D., Ph.D., Professor and Chair of Anesthesiology at the University of Rochester, is representing ASA and FAER as a co-chair of the ACTION Executive Committee. Robert H. Dworkin, Ph.D., Professor of Anesthesiology, Neurology, Oncology, and Psychiatry at the University of Rochester, is the Director of ACTION, and Dennis C. Turk, Ph.D., John and Emma Bonica Professor of Anesthesiology and Pain Research at the University of Washington, is the Associate Director. In addition to ASA, researchers and physicians from the American Academy of Neurology; American Academy of Pain Medicine; American College of Rheumatology; American Pain Society; Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; International Association for the Study of Pain; and Outcome Measures in Rheumatology; as well as representatives from the FDA, U.S. National Institutes of Health, the U.S. Department of Veterans Affairs, international initiatives, patient advocacy organizations, and a large number of pharmaceutical companies are participating in the ACTION public-private partnership.

Consistent with the aims and objectives of the FDA's Regulatory Science Initiative, ACTION was developed to provide a collaborative framework to undertake such analyses of analgesic trials and bridge gaps in the discovery and development of safe and efficacious analgesics.[4,5] Specific objectives include: 1) conducting analyses of databases of analgesic clinical trials; 2) developing novel methods for analyzing analgesic trial endpoints; 3) developing a "STandardized ANalgesic DAtabase for Research, Discovery, and Submissions" (STANDARDS) for the transformation and pooling of data from different analgesic trials; and 4) coordinating the public-private partnership and providing the infrastructure for supporting additional projects to inform analgesic development and trial design and to foster innovation in the development of improved pain treatments.

The modest progress to date in developing improved analgesics and the negative results of many recent clinical trials led to the development of this public health initiative. ACTION will provide the foundation for an evidence-based approach to the design of analgesic clinical trials by identifying relationships between trial characteristics and outcomes that could then be used in designing new trials. The focus will be on efforts to reduce false negative results and thereby increase assay sensitivity of clinical trials to show the benefits of efficacious treatments. Modifications in the design of analgesic trials have the potential to reduce the likelihood of false negative results and to maximize study efficiency (e.g., by requiring smaller sample sizes). Because assay sensitivity is related to the magnitude of the separation between improvements in the active treatment and placebo groups, an evidence-based approach to clinical trial design should also include an examination of relationships between study methodologic features (including patient characteristics) and placebo group responses. Importantly, assay sensitivity will only be increased if any efforts to reduce placebo group response do not have a comparable effect on responses to the active treatment.

The results of previous research suggest that various patient characteristics and research methods are associated with analgesic trial assay sensitivity or placebo group responses, or both. Unfortunately, relatively few studies have examined these relationships, and further research must be conducted to provide an adequate evidence base for any modification of the methodologic features on analgesic trials. In pursuing this objective, group level data across multiple clinical trials in large databases and individual trials with patient-level data considered separately and in pooled analyses will provide complementary information.

A major component of the ACTION initiative is the development of a public-private partnership, the mission

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of which is "to identify, prioritize, sponsor, coordinate, and promote innovative activities – with a special interest in optimizing clinical trials – that will expedite the discovery and development of improved analgesic treatments for the benefit of the public health." It is important to emphasize that the results of these activities will also be relevant to the development of improved pain treatments of all types, not just medications. We believe that the ACTION public-private partnership has the potential to greatly facilitate more efficient development of novel analgesic treatments and thereby improve the lives of patients with acute and chronic pain.

Links

1. Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) website: www.actionppp.org
2. FDA public-private partnership webpage for ACTION: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm231130.htm

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