

# Is Mechanism-Based Pain Treatment Attainable? Clinical Trial Issues

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**Abstract:** Woolf et al have recently called for the development of a mechanism-based pain taxonomy to guide the individualization of treatment based on each patient's pain mechanisms. Although any scientific physician could endorse this ideal, small academic clinical trials so far have failed to identify obvious differences in the response of different pain symptoms in the same condition to various drugs. In contrast, there are clear differences in the analgesic responses of patient groups distinguished on the basis of etiology or tissue origin of pain, factors which tend to be associated with groups of mechanisms. The few tests to diagnose pain mechanisms remain too delicate, time-consuming, or uncomfortable for general clinical use. To understand how best to exploit new mechanistic insights to assign treatments, one must scrutinize the relative value of diagnostic classifications based on etiology, tissue, and individual patients' pain characteristics in large clinical trials. Research priorities should include developing simple methods for assessing pain mechanisms in the clinic and increasing the efficiency of pain assessment methods in clinical trials. I describe a collaborative research agenda for academic pain researchers and funding agencies, the pharmaceutical industry, and regulatory bodies.

**Key words:** *Chronic pain, analgesics, pain measurement.*

From their first medical school courses in pathophysiology, physicians are taught to strive toward the ideal of treating individual patients based on inferences about their disease mechanisms. The prototypical disorder for this clinical method is heart failure. It was thrilling to realize, halfway through my internship, that with a glance at my patient's neck veins, a listen to the lung bases, and a feel of the liver and ankles I could estimate the pressures in each of the heart chambers and choose from a large array of medications that can alter intravascular volume, myocardial contractility, and vascular resistance to reduce symptoms. Individualized mechanism-based treatment has led to remarkable extensions of survival of patients with heart failure over the past 2 decades.

In other diseases, mechanism-based treatment has been elusive, either because the underlying mechanisms have been poorly understood or because of the lack of tools to determine mechanisms in individual patients. However, in many types of cancer and immune disorders, the inability to individualize treatment by inferring mech-

anisms in each patient has not precluded great therapeutic advances. In these illnesses, general mechanistic assumptions and treatments based upon animal models of disease have been applied to empirically defined groups of patients, and series of trials of single and combination therapies have often led to cure.

The relatively young field of pain research has been fortunate to identify peripheral and spinal sensory pathways that can be readily manipulated in animal models of many painful disorders, leading to a recent explosion in the understanding of pain mechanisms in animal models of disease. The cochairmen of this symposium, Clifford Woolf and Martin Koltzenburg, hope to make these insights the basis of everyday medical practice. To this end, they and their colleagues organized 2 recent meetings on the topic "Towards a Mechanism-Based Classification of Pain." These scientists argue that it is time to construct a mechanism-based pain taxonomy that can guide treatment according to the patient's pain mechanisms rather than rely upon standard diagnostic categories that refer to causative agents, underlying diseases, or duration of pain.

A pain editorial resulting from the first meeting was unimpeachable regarding the basic science but, as Harold Merskey pointed out, did not fully confront a major clinical limitation.<sup>1,2</sup> Our current diagnostic tools can make only a few types of mechanistic distinctions in patients, and

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most of these tests are too time-consuming, painful, or expensive for routine clinical practice. A more recent article by Woolf and Decosterd<sup>3</sup> admits this difficulty, and they reasonably scale back their proposal to a 2-tiered solution: intensive mechanistic studies in specialized research settings and the development of simple interview and physical examination techniques for large clinical trials and practice.

I doubt that a comprehensive mechanism-based pain taxonomy and treatment algorithm are close at hand. The main reason for my caution is that for 20 years, several clinical trial groups, including our own, have scrutinized responses of neuropathic pain to antidepressants, opioids, adrenergic agonists, and *N*-methyl-D-aspartate (NMDA)-receptor antagonists and have failed to find impressive differences in response to a particular drug between allodynia and ongoing pain and between paroxysmal and continuous pain, or among various pain qualities.<sup>4-10</sup> When the drug was effective, a broad range of patients responded, and most of the symptoms tended to get better. Although this suggests that mechanism-based differences might often be small, alternative explanations are that the measurement methods were weakly correlated to mechanism, the drugs were not specific enough, and the sample sizes were too small.<sup>11</sup>

In the long run, Woolf et al are correct: Once we have the requisite knowledge, individualized treatment driven by mechanistic inferences cannot fail to be safer and more effective than empirically based treatment. In this paper, I will offer a critique of their project that I hope will help us prepare for the major research program that they propose. Harold Merskey began the first International Association for the Study of Pain (IASP) Pain Taxonomy with a 2000-year-old Talmudic quotation: "It is not your duty to complete the work, but neither are you free to desist from it."<sup>12</sup>

## Patients Often Have a Mix of Pain Mechanisms

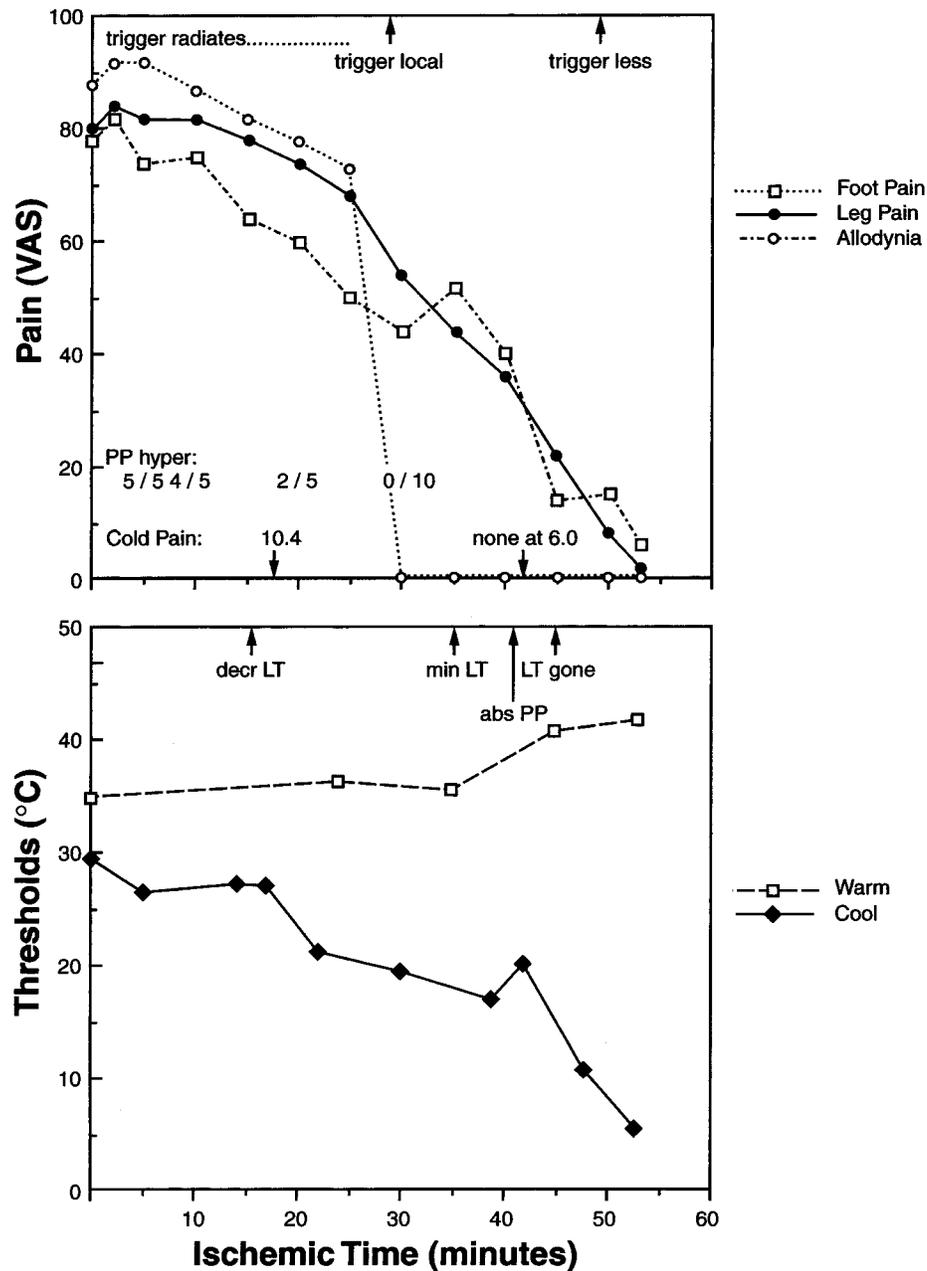
Animal studies show that a circumscribed injury triggers a collection of pain mechanisms, each of which might be sensitive to a different treatment. For example, an acute inflammatory insult causes sensitization of nociceptive primary afferents that might be blocked by inhibitors of prostaglandin production; sensitization of spinal dorsal horn projection neurons that might be blocked by NMDA glutamate receptor inhibitors; and after 24 hours, a phenotypic switch in A $\beta$  touch fibers, which now begin to produce the nociceptive transmitter substance P, sensitive to

NK-1 receptor blockers.<sup>13</sup> Focal nerve injury might trigger the same mechanisms but, in addition, produces ectopic discharge from new nerve sprouts and dorsal root ganglion (DRG) cells sensitive to sodium-channel blockers and ingrowth of sympathetic afferents whose release of norepinephrine can excite the DRG but are blocked by adrenergic antagonists.<sup>14</sup>

Most human diseases produce multiple injuries; therefore, they might have an even larger set of pain mechanisms. If the injury is located in a distal limb, intensive sensory testing in a specialized laboratory might directly show multiple mechanisms. Figure 1 (Max and Byas-Smith, unpublished data) illustrates observations made during an ischemic block of the leg in a patient with chronic mechanical allodynia and hyperalgesia in large areas of the leg after fracture of a small foot bone. After 20 to 30 minutes of ischemia, decrease in light touch perception and cool detection threshold (bottom panel) with preserved warm thresholds indicates selective blockade of myelinated A $\beta$  and A $\delta$  fibers. During this time, mechanical allodynia and widespread radiation of pain from pressure over the healed fracture site abruptly disappeared, indicating these pains were dependent on myelinated fiber input. Dull, localized pain and tenderness at the fracture site persisted for 55 minutes and diminished as threshold for warm detection rose, suggesting that this pain was largely mediated by unmyelinated C fibers. An infusion of ketamine, but not saline or phenolamine, completely relieved all varieties of pain, allodynia, and hyperalgesia in this patient, consistent with involvement of NMDA glutamate receptors but only at dose levels producing unpleasant dissociative effects.<sup>9</sup>

A series of other tests provided clues to additional mechanisms. Disappearance of allodynia in the femoral nerve territory after local anesthetic nerve block of the fracture site, well within the sciatic nerve territory, suggested altered processing of light touch input in spinal neurons that received these 2 convergent inputs. Elicitation of pain by an electrical stimulus at the detection threshold for touch suggests that A $\beta$  fibers, which are the most easily activated by electrical current, can trigger pain.<sup>15,16</sup> A positron emission scan showed hypoperfusion in the thalamus contralateral to the painful leg, suggesting altered supraspinal processing.<sup>17</sup>

This series of tests consumed more than a week, caused the patient considerable discomfort, and clearly would not have been possible in a usual practice setting. However, this laboratory workup, like studies that have been performed by many research groups, shows that clinical pain is often the result of many mechanisms.



**Figure 1.** Quantitative sensory testing during ischemic block of the leg of a patient with complex regional pain syndrome; type I shows multiple pain mechanisms. (Top panel) Ongoing boring pain at old fracture site in lateral foot (dotted squares), burning pain in medial thigh (solid circles), and mechanical allodynia in medial thigh (open circles) are plotted against time. (Bottom panel) Detection thresholds for warm (broken line) and cool (solid line) are plotted against time. A decrease in the cool detection threshold at 20 minutes suggests that blockade of myelinated A $\delta$  fibers begins at this time, whereas a rise in the warm detection threshold at 40 minutes suggests blockade of C fibers, which are more resistant to ischemia than myelinated fibers. Mechanical allodynia disappears at 30 minutes, during the period of progressive myelinated fiber block, suggesting that myelinated fiber function is essential for allodynia to occur. At the same time, the radiating pain that follows pressure on the fracture site also disappears (top of upper panel) and light-touch sensation almost disappears (top of bottom panel). Part of the foot and leg pain persists until the onset of C-fiber blockade, suggesting that C fibers are sufficient to mediate this pain. VAS, visual analog scale; PP, pinprick; hyper, hyperalgesia; decr, decreasing; LT, light touch; min, minimal; abs, absent.

## Even the Most Selective Drugs Affect Multiple Types of Pain

Table 1 shows the effects of intrathecal spinal injection of 22 classes of analgesics in commonly used animal models used as probes of various pain mechanisms.<sup>18</sup> These include models of acute

thermal stimulation of normal skin such as the hot plate and tail flick assays, models involving injection of chemicals that damage soft tissue and joints, and chronic neuropathy and spinal cord injury models. Although there are differences in the spectrum of response, opioids, NMDA and 2-amino-3-hydroxy-5-methyl-4-isoxazole-propionic

**Table 1. Summary of Spinal Drug Effects as a Function of Preclinical Pain Models**

DRUG	FACILITATED			NEUROPATHIC				
	ACUTE HP/TF	INFLAMED		BENNETT (THERMAL HYPERALGESIA)	CHUNG (TACTILE ALLODYNIA)	INTRATHECAL STRYCHNINE (TACTILE ALLODYNIA)	STREPTOZOCIN DIABETES (TACTILE ALLODYNIA)	SPINAL ISCHEMIA (TACTILE ALLODYNIA)
		FORMALIN (FLINCHING, PHASE 2)	PAW OR KNEE (THERMAL INJURY/PRESSURE)					
Agonist								
Opioid								
μ	+	+	+	+	0	0	+	0
δ	+	+	+	+		0		
κ	+	+	+	+		0		
ACH								
Muscarinic	+	+						
Nicotine	+							
Adrenergic-α <sub>2</sub>	+	+	+	+	+	0	+	0
GABA								
A	+	+	+	+			0	
B	+	+	+	+				+
5-HT	+		+					
Adenosine								
A1	+	+		+	+	+		
Neuropeptide								
Y	+							
Antagonist								
NMDA	0	+	+	+	+	+	+	0
AMPA	0	+	+	+	+			+
NK1	0	+	+	0			+	
Inhibitor								
COX	0	+	+				+	
NOS	0	+	+	+				+
ACHase	+	+						
Enk-ase	+	+	+					
Channels								
Intravenous sodium								
Calcium	0	+		+	+		+	+
L	0	+			0			
N	0	0+			+			
P	0	+			0			

Abbreviations: HP, hot plate; TF, tail flick.

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acid (AMPA) glutamate antagonists, nitric oxide synthetase inhibitors, and adenosine and adrenergic agonists have some effects across many pain models. This overlap of effects, appreciable with the most highly selective drugs and animal models, should be far greater in the clinic, where broader spectrum drugs are used and patients' pains have not been produced by uniform lesions.

To validate and derive therapeutic benefit from any mechanistic-based pain taxonomy, we will need to carry out clinical trials comparing various drug classes with each other and across diagnostic classes. The preceding arguments (that even well-defined mechanistic models in animals might have modest differences in drug response and that patients have a mix of pain mechanisms) imply that the differences between effects will be small. Sample size formulas for

clinical trials show that the number of patients needed to detect a particular treatment difference rises with the inverse square of the treatment difference one wishes to detect.<sup>19</sup> The usual clinical trial to distinguish an analgesic from placebo enrolls 50 patients per group. Cherny et al<sup>20</sup> analyzed data from 474 morphine or heroin injections during randomized, controlled trials in cancer patients and estimated that the net analgesic effect was 25% smaller in patients with neuropathic pain than in patients with somatic pain. Therefore, a study powered to detect a treatment difference this small would require  $1/(1/4)^2$ , or 16, times the usual number of patients needed to distinguish opioid from placebo, or 900 patients per group!

This point, which has been forcefully argued by Moore et al,<sup>21</sup> means that clinical trials to vali-

date a mechanism-based classification will need to be large and multicentered, involving personnel without extensive expertise in quantitative sensory evaluation. Therefore, tests to identify pain mechanisms must be simple. It is essential to boost the power (decrease the variability) of clinical trials by making wider use of crossover studies and addressing the little-studied question of what type of pain questionnaire is most sensitive in studies of chronic pain.<sup>22,23</sup>

## The Crisis in Clinical Analgesic Development Is Already Here

Most academic and industrial pain researchers and drug regulators agree that the conventional pathways for clinical analgesic development and labeling are obsolete because they ignore the heterogeneity of pain mechanisms. The standard clinical development path arose from studies in the 1950s, when analgesic pioneer Henry Beecher<sup>24</sup> wrote that (in assessing analgesics in humans) “neither source of pain nor type (acute or chronic) are important considerations.” The current US Food and Drug Administration (FDA) guidelines, issued in 1979 and slightly revised in 1992, reflect this view that “pain is pain.”<sup>25</sup> They state that 2 positive controlled trials in any 2 pain conditions, plus the appropriate safety data, will qualify a drug to be marketed “for the relief of pain.” This principle served reasonably well through the 1980s when new analgesic approvals were limited to broad-spectrum opioids and aspirin-like drugs. However, the recent proliferation of experimental analgesics targeted at specific pain mechanisms has led regulatory leaders to begin to seek academic advice for a major rewriting of analgesic development guidelines.

This issue is complicated by the fact that there are 3 major questions about analgesic efficacy that must be answered to provide the clinician with a rationale for drug choice. The first is whether the putative analgesic has any efficacy: Can it surpass placebo in a homogeneous group of patients? The second issue is generalizability: Which of the broad range of pain patients seen in clinical practice will it help? The third is comparative: Where do the drug’s efficacy and side-effect profile place it in comparison to other analgesics? Proof of efficacy is the major goal of most development programs. To show that a drug relieves pain more effectively than a placebo in 1 or 2 pain conditions is sufficient evidence for analgesic approval under current FDA regulations.<sup>25</sup> Study efficiency is the overriding goal in the design of these studies; one seeks clinical conditions with the least variability, most robust response, and most rapid and inexpensive enrollment. Generalizability to the broad gamut of

patients seen in the clinic is hardly addressed in regulatory guidelines because the underlying assumption has been that all pains are the same. Most current practice in the pain clinic is now based on results in the efficient third molar extraction model, but in the absence of clinical trials in most chronic pain conditions, we cannot say whether this is a reasonable or a ludicrous way to proceed.

The 1992 FDA guidelines for clinical studies of analgesia require comparison of a new drug with at least 1 standard analgesic in single-dose studies but say nothing about the repeated dose-efficacy studies that are the best way to examine many of the new drugs for neuropathic pain. In some current pharmaceutical industry studies of chronic pain, the FDA has not required companies to include an active comparator.

It might take many years to develop rigorous new clinical tests of pain mechanisms and correlate these with the results of simpler assessments that can be used in large clinical trials. In the meantime, how might we learn to more appropriately generalize the results of clinical trials to the broader mix of patients seen in practice without making the cost of clinical drug development prohibitive? One interim step is that new analgesics be studied in pain syndromes arising from a variety of different tissues.

## Does the Pain’s Tissue of Origin Make a Difference in Analgesic Response?

Using well-validated principles of medical diagnosis, it is usually possible to make at least a good guess about the type of tissue giving rise to pain. Pain clinicians have been particularly interested in differentiating pain arising in nerve from other pains because several classes of drugs (eg, tricyclic antidepressants, anticonvulsants, systemically administered local anesthetics, and  $\alpha$ -2 adrenergic agonists) appear to help neuropathic pains more than other pains. In an open-label study of 111 patients, Galer et al<sup>26</sup> found that lidocaine infusion reduced pain in 87% of patients with definite peripheral nerve lesions but in only 33% of patients with pains of other origins, presumably because this drug blocks sodium channels expressed on injured nerve. Some muscle pains also appear to have distinct pharmacologic responses. For example, fibromyalgia appears quite sensitive to tricyclic antidepressants but insensitive to nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>27,28</sup>

In published reports, Woolf et al<sup>1</sup> and Woolf and Decosterd<sup>3</sup> only briefly mention the tissue origin of pain. They downgrade this factor as a basis for pain diagnosis because, as in etiologic diagnosis, the tissue of origin does not directly

**Table 2. Pain Research Remains Clustered in a Few Disease Areas, While Common Conditions Are Overlooked**

<i>NIH CLINICAL PAIN RESEARCH GRANTS, 1996 (UNOFFICIAL CRISP SEARCH, M. MAX)</i>		<i>MEDICAL SPECIALTIES REPRESENTED IN THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN, JANUARY 2000</i>		<i>PAIN COMPLAINTS AMONG THE 20 MOST FREQUENT REASONS FOR VISITING THE DOCTOR (AMERICAN ACADEMY OF FAMILY MEDICINE, 1987)</i>
<i>DISEASE</i>	<i>NUMBER OF GRANTS</i>	<i>SPECIALTY</i>	<i>NUMBER OF MEMBERS</i>	
Cancer	21	Anesthesiology	2850	Back pain
Neuropathic pain	17	Neurology	297	Headache
Chronic orofacial pain	11	Rehabilitation medicine	234	Abdominal pain
Low-back pain	10	Dentistry	231	Chest pain
Headache	9	Psychiatry	119	Neck pain
Postoperative and burn pain	9	Rheumatology	75	
Pediatric pain, miscellaneous	7	Oncology	61	
Sickle cell pain	6	Orthopedics	59	
Arthritis	6	Obstetrics & gynecology	18	
Muscle pain, fibromyalgia	3	Urology	13	
Gastrointestinal pain	2	Cardiology	8	
Cardiac pain	1	Gastroenterology	8	
Labor/gynecological pain	1	Ear, nose, and throat	3	
Urological pain	1			
Neck pain; ENT pain	0			

NOTE. Mismatch of the distribution of clinical research (left) and researchers (center) when compared with the distribution of common pain complaints (right). The dearth of pain research related to the cardiovascular, gastrointestinal, urological, and female reproductive organ systems, which account for much chest and abdominal pain, is particularly striking.

specify mechanism. However, many other neurobiologists claim that there might be some mechanistic differences among pains arising from different tissues. The unique anatomic consequences of nerve injury need no further comment, but several lines of evidence now make it plausible that visceral pains will respond somewhat differently to drugs than would other pains. For example, Willis et al<sup>29</sup> claim that pelvic visceral pain is unique because of dorsal post-synaptic tract involvement; Gebhart<sup>30</sup> suggests that visceral receptors are less specialized than cutaneous receptors and may differ in response to drugs; and a review by Levine et al<sup>31</sup> suggests that a higher proportion of visceral afferents than somatic afferents are rich in peptide neurotransmitters.

Although lesions in each tissue can cause pain by many peripheral, spinal, and supraspinal mechanisms, the tissue of origin might bias the outcome toward a particular mix of mechanisms, with implications for drug therapy. Unlike specific patient-by-patient mechanistic diagnosis, which might take decades to achieve, tissue diagnosis can be incorporated into therapeutic decisions right now. The limitation is that industry and academic clinical trials, and clinical pain research in general, have been limited to a few diseases. Table 2 shows the distribution of National Institutes of Health (NIH) clinical pain research grants (an unofficial hand search of the Computer Retrieval of Information on Scientific Projects [CRISP] database performed

in October, 1996); the specialty distribution of the physician membership of the IASP; and the 5 most common pain complaints encountered in US doctors' offices.<sup>32</sup>

Note that clinical research grants and pain society membership appear to cluster in a few specialties: anesthesiology, neurology, neurosurgery, dentistry, and oncology. My historical interpretation is that these were the specialties represented at the first meeting of the IASP. Even though abdominal pain, chest pain, and neck pain are among the most common pain complaints in practice, we have failed to recruit many interested clinicians and to secure relevant federal research grants. With their eyes on short-term costs and returns, industry scientists are reluctant to carry out clinical trials in a pain condition until NIH-funded academic investigators have performed the preliminary work to show feasibility and estimate sample sizes.

On the other hand, maybe Beecher<sup>24</sup> and the modern-day "lumpers" are mostly right. Perhaps studies of third molar extraction will predict relative analgesic efficacy for pain arising from many tissues over a broad range of drugs, and we don't need to develop costly new models. Alternatively, perhaps we need new chronic pain models, but trials in pain arising from many tissues and disease states will reveal recurrent patterns of correlation, so that studies in only a few new models will tell the whole story. We will not know until a range of drugs has been studied in pain arising from many tissues.

## Organizational Issues

The discussion above has suggested that academic pain researchers, the pharmaceutical industry, NIH, and FDA each has a piece of the puzzle. Industry has the specific new drugs and enrolls the large patient populations in their trials that could make it possible to discern modest differences between different drugs or patient subgroups. However, pharmaceutical companies do not have an incentive to spend years validating new measurement tools or developing new disease models for clinical trials. The long-term perspective and public health mission of NIH and academic pain researchers are suited to the latter 2 tasks, but funds for large clinical trials are limited and access to detailed data from industry trials is not available. The FDA sees the most data pertaining to novel analgesics and might have the best intuitive grasp of emerging problems, but it has little or no protected research time to confirm and publish these ideas. The FDA's requirements and wishes regarding clinical trials also get close attention from industry, although an increase in the regulatory burden might trigger a political backlash.

## Recommendations

I would suggest a coordinated approach by academic and industry pain scientists, FDA regulators of analgesics, and industry that would include the following:

### 1. NIH would solicit research proposals

- (A) To develop and show the reliability and validity of methods to measure aspects of pain likely to correlate with mechanism and easily assessed in large clinical trials or in practice.<sup>3</sup> These variables might include pain quality, summation with repeated stimulation, response to walking and other movements, and measurement by simple quantitative stimuli, such as light brush or electrical stimulation.<sup>33-35</sup>
- (B) To compare the relative efficiency of different pain assessment methods for distinguishing treatment efficacy in chronic studies. These might include comparing paper or electronic diaries with single retrospective measurements and numerical or VAS scales with lists of descriptors for pain intensity or relief.
- (C) To establish populations of patients with chronic pain arising from tissues and diseases rarely studied in analgesic trials, particularly

the subtypes of visceral pain. A committee of these academic investigators might offer these populations as an NIH-funded "add-on" to industry studies of interesting new analgesics.

**2. Industry would agree to incorporate some of the measurement tools described above into their trials and make individual patient data available to the community of researchers as soon as this would not jeopardize their competitive position.**

**3. FDA, in collaboration with NIH, academic pain researchers, and industry, would consider how to revise clinical analgesic development policies in a way that would provide incentives for novel industry approaches and encourage a greater understanding of mechanisms without inflating the cost of development. Some specific issues might include the following:**

- (A) Crossover studies, now rarely conducted in research intended for FDA review, should be encouraged in chronic pain studies, because these will provide far greater power to make distinctions between drugs or subgroup response that are relevant to pain mechanism. Crossover studies regularly provide power equivalent to parallel group studies with 5 to 10 times the patient number.<sup>36</sup> These fell out of regulatory favor because statisticians were concerned about the possibility of spurious conclusions resulting from carry-over effects. Some recent statistical work has challenged these critiques, but these concerns could be rendered moot by requiring some proof of efficacy from between-patient comparisons from first treatment data.<sup>37</sup>
- (B) Development programs for analgesics intended for repeated dosing should include a comparison with at least 1 of the standard drugs used in that particular patient group. Superiority to the comparator would not be required for approval; this is just meant to better inform the clinician.
- (C) Treatment with drug combinations is the logical consequence of mechanistic diagnosis, but there have been virtually no analgesic combination studies in chronic pain. The FDA should revisit their policies on combination drugs, with particular attention to chronic pain. NIH and the FDA should consider how to encourage and fund such studies.

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