

Mechanism-based Pain Diagnosis

Issues for Analgesic Drug Development

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ENORMOUS progress is currently being made by the exploitation of modern neurobiologic techniques in the elucidation of mechanisms that may contribute to the pathogenesis of pain.¹⁻³ These indicate that pain can be generated in multiple ways at a number of different sites that may coexist between and across diverse disease states.^{4,5} Molecular biologic techniques are contributing to the analysis of pain mechanisms and are leading to the discovery of new targets, which are being used in high throughput screens by the pharmaceutical industry for the discovery of highly specific small molecules as potential novel analgesics. The discovery of targets specific to particular pain mechanisms will soon enable therapy to be targeted specifically at those mechanisms. This raises several problems: how to identify the mechanisms in an individual patient, how to test for the efficacy of a compound that may alter only one component of a complex syndrome that involves multiple mechanisms, and how to test for interaction between two different compounds targeted at two independent mechanisms. Clinical studies suggest that within conventional diagnostic groups of chronic pain patients, there are subgroups with differing responses to drug treatment,⁶⁻⁹ and yet the clinical development of new analgesic drugs has ignored this mechanistic heterogeneity. Trials that select patients based only on a disease may produce a false-negative result, with the nonresponders

diluting out the benefit in the subgroup with the targeted mechanism.

In this review, we sketch a research agenda that might move us toward a mechanism-based analgesic development. First, it is necessary to consider the following questions: To what degree can clinicians directly assess pain mechanisms in patients? What is the evidence from controlled clinical trials that variation in analgesic response between patients can be explained by disease or syndrome, tissue of pain origin, or symptom-based assessment of pain mechanisms? How should analgesic development pathways be revised to most efficiently demonstrate the spectrum of efficacy of a new drug? What types of collaborations between academic pain researchers, industry, government research funders, and regulators can hasten the potential clinical benefits of mechanism-based pain treatment?

Mechanism-based Pain Diagnosis

Pain is not a discrete sensory experience that is switched on only by a particular or identifiable set of "pain" stimuli acting on a unique or stable "pain" pathway to elicit an invariant sensation. Instead, pain is a diverse set of complex perceptual events that are characterized by their unpleasant or distressing nature. Although, from our everyday experience, we tend to associate pain only with an intense or noxious peripheral stimulus, in most patients, pain arises either in the apparent absence of any peripheral input (spontaneous pain) or in response to low-intensity or innocuous stimuli that are usually not associated with pain (allodynia). The induction of pain encompasses multiple different neurobiologic components originating in a complex fashion from mechanisms that may manifest and interact at many different levels of the neuraxis and that are inherently dynamic or changeable. Although global outcome measures such as a simple visual analog score or categorical scale may provide a crude integrated measure of the total pain experienced by the patient, the mechanisms responsible for the pain, or possibly more important, the differential response of some mechanisms and not others to a particular treatment, cannot be identified using these measures. That is not to say that the overall clinical aim should not be to relieve the global pain experience and its associated unpleasantness and discomfort, but that a more rational way of achieving this may be to identify what mechanisms contribute,

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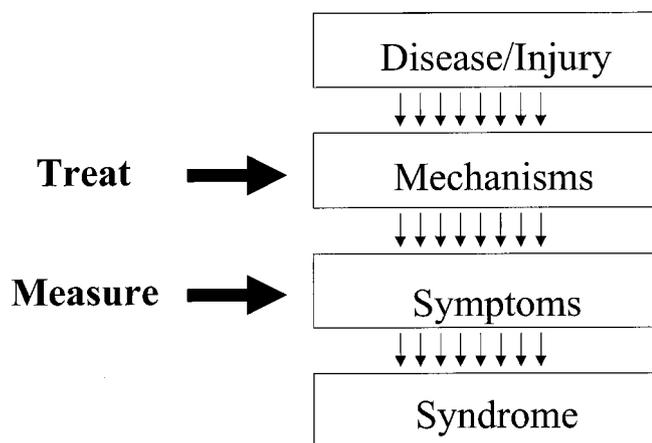


Fig. 1. A diagrammatic representation of the relation between etiologic or disease factors, mechanisms, symptoms, and pain syndromes. This relation holds both for pain syndromes in human patients and animal models of pain conditions. The ideal for pain management is to treat the mechanisms (apart from disease-modifying therapy). The problem is how to identify these mechanisms. At present, our only indication is the symptoms generated by the mechanisms, which, however, are not equivalent to mechanisms.

target treatment specifically at these mechanisms, and measure the effect of such treatment.

The major challenge in attempting any mechanism-based assessment of pain is to identify in a particular patient what mechanisms operate to produce the symptoms experienced by the patient and then use this to determine rational treatment (fig. 1). The conventional approach has been to analyze patients on the basis of common etiologies or diseases on the assumption that a single disease will operate to produce pain by single or at least common mechanisms. This approach groups patients into categories, such as post herpetic neuralgia, postsurgical pain, or osteoarthritic pain. When a common disease is not easily identifiable, *e.g.*, idiopathic low back pain, the patients tend to be classified on the basis of the anatomic referral pattern of the pain. Although such an approach has utility, it ignores the possibility that a single etiologic factor may produce pain by diverse mechanisms, which may occur singly, sequentially, or together. Individual patients may have multiple mechanisms operating both serially (in a temporal sequence depending on the natural history of the etiologic disease and the reaction of the nervous system to it) and in parallel. How can we go about identifying pain mechanisms? A good starting point is to know what mechanisms can potentially produce pain. This is an area in which there have been rapid advances over the past decade, although our understanding still remains incomplete.

Key Features of Pain Mechanisms

Different aspects of pain are likely to be mediated by different input channels. What input signals initiate the

chain of sensory processing that lead to the experience of a conscious awareness of pain? Until recently, a common view was that the pain system was a fixed label-line system activated in the periphery only by nociceptors in response to an adequate noxious stimulus. Although this is true of nociceptive pain (pain evoked by a noxious stimulus) in normal circumstances, it is certainly incorrect for pain hypersensitivity or spontaneous pain, where a number of different input channels can lead to the pain sensation, including (1) nociceptor activation in the periphery by noxious mechanical-thermal or chemical stimuli (nociceptive pain); (2) activation of sensitized nociceptors in the periphery by low-intensity stimuli (peripheral sensitization); (3) ectopic discharge in nociceptors originating at a neuroma-dorsal root ganglion-peripheral nerve-dorsal root (peripheral nerve injury); (4) low-threshold afferent activation in the periphery by low-intensity mechanical-thermal stimuli (in combination with central sensitization, synaptic reorganization, or disinhibition); (5) ectopic discharge in low-threshold afferents originating at a neuroma-dorsal root ganglion-peripheral nerve-dorsal root (peripheral nerve injury associated with central sensitization, synaptic reorganization, or disinhibition); and (6) spontaneous activity in central neurons (in the dorsal horn, thalamus, or cortex). It is important to try to identify the particular input channel responsible for generating a particular pain because this represents the first anatomic target for treatment.

The pain evoked by different input channels represents operation of multiple mechanisms: (1) activation of high-threshold receptor-ion channel transducers in nociceptor peripheral terminals (nociceptive transduction); (2) change in threshold-sensitivity of receptor-ion channel transducers in nociceptor peripheral terminals (peripheral sensitization); (3) changes in ion channel expression-phosphorylation-accumulation in primary afferents (altered sensory neuron excitability); (4) post-translational changes in ligand- and voltage-gated ion channel kinetics in central (spinal cord and brain) neurons, changing their excitability and the strength of their synaptic inputs (central sensitization); (5) alterations in the expression of receptors-transmitters-ion channels in peripheral and central neurons (phenotype modulation); (6) modification of synaptic connections caused by cell death or sprouting (synaptic reorganization); and (7) loss of local inhibition at different relay levels in the neuraxis and of descending inhibition originating in the forebrain and brainstem and terminating in the brainstem and spinal cord, caused by decreased activation of neurons, downregulation of receptors-transmitters, and cell death (disinhibition).

A considerable amount is known about the mechanisms that operate in primary afferent and dorsal horn neurons to produce pain. Much less is known about the changes that occur in the brain and how the effective, cognitive, and perceptual aspects of pain are generated.

However, it is clear that the sensory cortex can undergo considerable plasticity in concert with the changes that occur in subcortical structures, and such supraspinal plasticity is likely to play a major role in shaping the pain experience.

Pain can be assessed at a number of different levels: society (economic cost, effect on the family unit), the individual (personal suffering), the system (how the pain is generated by the peripheral and central nervous system), and cells and molecules (the particular change in the individual elements of the system that initiate and maintain the pattern of functioning that expresses itself as pain). Pain must be seen in the context of all of these different levels of expression if we are to truly understand the mechanisms responsible. Although pain has an important psychological component, which needs to be an element of any treatment strategy, this review concentrates on pain as a sensory experience, because it is here that rapid progress has been made in identifying specific mechanisms.

Drug Development and Pain Mechanism

Drug development involves several key steps:

1. establishment of a biologic hypothesis of the mechanisms involved in the pathophysiology of pain (e.g., that prostaglandin E₂ release from inflamed tissue contributes to the peripheral sensitization of nociceptors)¹⁰;
2. identification of a potential molecular target based on the biologic hypothesis to screen for new analgesic compounds (e.g., inhibition of the inducible enzyme cyclooxygenase COX-2 will prevent prostaglandin E₂ production)¹¹;
3. establishment of a screen to look for small molecules that bind with high affinity to the target (and, in the case of COX-2, inhibit its action);
4. chemical optimization of any chemical "hit" to produce a series of lead compounds that will interact with high affinity with the target, but not others (selectivity) that are not likely to be toxic, have bioavailability, or pharmacokinetic problems, which are economic to produce and can be protected by patents;
5. test of the lead compound in animal models of pain to confirm or refute the original hypothesis and evaluate for efficacy and potential side effects;
6. test of safety in humans and establish pharmacokinetic properties (in some cases, surrogate pain models can be used to look at efficacy in volunteers; phase 1);
7. test of efficacy in small groups of patients (proof-of-concept testing; phase 2);
8. performance of large-scale multicenter clinical trials to assess efficacy and safety in a number of diverse clinical conditions (phase 3).

A mechanism-based approach to pain has implications for these steps at a number of levels. First, it will contribute to the development of valid hypotheses and therefore improve target selection. Second, it will assist the development and analysis of animal models suitable to test the effect of any chemical lead on a particular mechanism. Finally, it will assist the design of clinical trials for evaluation of efficacy. For both animal models and clinical trials, the key concern needs to be how or if one can infer the action of a particular drug on a given mechanism. In both cases, two key issues are selecting the patient population–animal model that expresses the mechanism and identifying what outcome measures can be used to identify if the treatment has altered the pain mechanism.

Pain Mechanisms and Animal Models of Pain

The imperative in developing laboratory animal models of pain has been to try to reproduce or mimic pain in humans. To this end, a number of tests have been devised to evaluate basal pain sensitivity, *i.e.*, the reaction of a normal or naive animal to graded-strength mechanical, thermal, or chemical stimuli (nociceptive pain). Beyond basal sensitivity, the aim has been to duplicate, within strict ethical limits, clinical pain syndromes, notably, inflammatory pain and neuropathic pain. For inflammatory pain, a wide range of inflammation-inducing agents and procedures have been applied to induce cutaneous, soft tissue (including skin, subcutaneous tissue, muscle, synovium), peritoneal, and visceral inflammation to mimic sunburn, acute postsurgical pain, acute soft tissue inflammation, monoarthritis, autoimmune polyarthritis, peritonitis, cystitis, colitis, and so on. For neuropathic pain, the peripheral and central nervous system have been damaged in a number of different ways, including experimental diabetes, peripheral neuritis, complete or partial nerve lesions, and spinal cord injury. Attempts have also been made to model cancer pain by inducing experimental tumors. Most of these models of pain rely on detecting a change in the threshold or response to an applied stimulus (stimulus-evoked pain); there are very few reliable measures of spontaneous pain, a major component of clinical pain.

The criteria for a successful animal model, particularly from an industry perspective, have unfortunately been more ones of convenience and reliability than detection of particular pain mechanisms. In many models, the end point selected to test a drug action has been, for example, a change in the reaction to a warm stimulus whether applied by contact or radiant heat (heat hyperalgesia), because this is simple to perform and measure and enables a relatively high throughput drug testing program. The data are then usually recorded as a positive or negative result in a particular model without consideration of what actual mechanism the drug may be influencing and without an explicit appreciation that each of

the animal models is the expression of multiple mechanisms, each of which may need to be detected with different outcome measures. Heat hyperalgesia is very rarely a clinical problem in humans, and the issue then is whether a compound that acts on this end point in an animal model will have any useful clinical action in patients. The answer almost certainly is that if this is the only action of the compound, if it leaves mechanical sensitivity or spontaneous pain unaffected, it will have very limited utility except in a very small subpopulation of patients. The predictive value of any animal model resides then both in which mechanisms are involved and what end points are measured.

It is essential that animal models are viewed not as models of human disease, as in most instances they are actually different, but rather as tools to help dissect out the relative contribution of different pain mechanisms in changing an animal's behavior in a given situation. We need ways of assessing if a drug acts *via* a particular mechanism involved in the generation of pain. The end of the preclinical drug development program should provide information on whether the drug has an action on basal pain sensitivity or the altered sensitivity present in inflammatory, cancer, and neuropathic models, if it acts on nociceptor terminals to block transduction, on axons to block conduction, or in the central nervous system to modify transmission. To do this, multiple models with a number of different end points should be used in a matrix fashion. There is also limited information on how well a compound should be expected to perform in animal models before it should be selected for study in patients. Do you need a 100% reversal or is 50% good enough? Because nonlocomotor central nervous system side effects (nausea, dizziness) are difficult to detect, a greater efficacy may be demonstrable in animals than in humans, where such side effects will often limit the maximum dose tolerated.

Difficulties of Identifying Precise Pain Mechanisms in Humans

At present there is broad agreement among pain clinicians and basic scientists that no diagnostic tools are available to unambiguously identify which mechanisms are present in a given patient, never mind which molecular targets are responsible. The only option we have at the moment is to analyze patients on the basis of symptom clusters rather than just on disease (fig. 1). The assumption here is that common mechanisms initiated by diverse etiologic factors may elicit common pain symptoms. Patients grouped on the basis of shared symptoms may include the following categories: (1) spontaneous pain, which may be continuous or intermittent, superficial or deep, and which may elicit different subjective sensations described as burning, shock-like, ach-

ing, *etc.*; or (2) stimulus-evoked pain, or pain evoked in response to mechanical, thermal (cold and heat), or chemical low- or high-intensity stimuli applied statically or dynamically to skin, joints, bone, muscle, or viscera.

A combination of studies using animal models and human investigations has identified some potential associations between particular mechanisms and particular symptoms: (1) a reduction in the pain threshold to heat stimuli applied directly to a site of inflammation and peripheral sensitization; (2) tactile allodynia in a noninflamed area and an *N*-methyl-D-aspartate (NMDA) receptor-mediated central sensitization; (3) spontaneous burning pain and C-fiber activity; and (4) paraesthesia and ectopic A fiber activity.

Although it is clear from available studies that particular mechanisms may be sufficient to elicit associated symptoms, it is less clear whether they are always necessary. In other words, what confidence can we have that a given symptom reveals the presence of a defined mechanism? The answer at the moment is that we know too little of the numerous mechanisms that may potentially produce pain and even less about their coupling with individual symptoms. Although tactile allodynia may reflect central sensitization, it is conceivable that it may also result from central disinhibition and a sprouting of low-threshold afferent terminals in the dorsal horn. Nevertheless, in the absence of other diagnostic approaches, it is important for clinical trials to be designed to collect as much information as possible about symptom clusters and their differential expression and responsiveness to specific highly targeted treatment (fig. 1). It needs to be recognized, however, that different pain mechanisms are not independent and that even highly targeted treatment may alter multiple outputs. A decrease in ectopic activity in primary sensory neurons produced by a specific sodium channel blocker, for example, may directly decrease spontaneous pain but may also reduce the secondary tactile allodynia that results from the central sensitization in the spinal cord activated by the ectopic input. Furthermore, drugs that act on different molecular targets may produce similar outcomes in terms of symptoms. A sensory neuron-specific sodium channel blocker and a drug that acts on the presynaptic terminal of primary afferents to block transmitter release may both reduce spontaneous pain.

Have Distinctions among Pain Symptoms or Pharmacologic, Tissue, or Disease Diagnoses Explained Differences in Response to Analgesics?

Symptoms as an Indicator of Mechanism

Clinical investigators have tried for two decades to find different responses of symptoms in analgesic drug trials, particularly in studies of chronic neuropathic pain. To our knowledge, the single success to date has been the

demonstration that postherpetic neuralgia patients with allodynia and no sensory loss respond to topical anesthetics, whereas patients with major sensory loss do not.⁹ Studies of opioids,¹² tricyclic antidepressants,¹²⁻¹⁴ clonidine,⁷ and gabapentin¹⁵ in neuropathic pain have failed to identify characteristics of patients or pain symptoms more likely to respond to treatment. Steady and paroxysmal pain, allodynia, and pain of various other qualities tended to be reduced in parallel, and quantitative sensory testing has not been illuminating,^{16,17} although this may reflect the insensitivity or inappropriateness of the outcome measures used.

Recent clinical trials in postoperative patients suggest that it may be informative to separately assess pain at rest and several types of evoked pains. Stubhaug *et al.*¹⁸ reported that very-low-dose ketamine infusion reduces the area and intensity of mechanical hyperalgesia around a nephrectomy incision through day 7, although it had little effect on overall pain after the first postoperative day. In postoperative dental pain, the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-kainate glutamate receptor antagonist LY 293558 has minimal effects on resting pain but has a robust effect on pain evoked by mouth opening.¹⁹ Movement-evoked postoperative pain is more resistant than rest pain to the effects of either local anesthesia of the surgical wound or intravenous fentanyl.^{20,21} Because movement-evoked pain limits rehabilitative efforts and everyday activities, a drug that disproportionately blocks movement-evoked pain would be potentially valuable but might be dropped early in development after negative acute pain studies that assessed only pain at rest. The traditional way of conducting postoperative pain studies is to let the study nurse choose either a resting state or pain-provoking maneuver to adjust baseline pain to a moderate-to-severe level,²² a method that makes it impossible to infer the mechanism of the pain.

Adoption of multiple evoked pain measures will require work to standardize and validate the methods. Even in postoperative dental pain, the most common screening model for new analgesics, little work has been performed on evoked pain. These measures might include pain evoked by standardized movement and static and dynamic mechanical stimuli.²³ Electrical stimuli near the wound can selectively activate A- β fibers even in the presence of sensitized C nociceptors.^{24,25} Administration of stimuli closely spaced in time can test for wind-up of pain.²⁶ Woolf and Decosterd²⁷ suggested a list of pain symptoms that could be quickly assessed in a brief evaluation, but its utility or sensitivity for identifying different evoked pain clusters needs to be validated.

Pharmacologic Diagnosis of Pain Mechanism

Although the ideal of pain researchers has been to infer mechanism from a sensory test and then choose drug treatment accordingly, there has been a bit more

success in using drugs themselves as a probe of mechanism. In small groups of patients, pain relief after a brief infusion of opioid⁸ or lidocaine²⁸ has predicted subsequent response to long-term treatment with opioid or mexiletine. Although clinicians have used other types of drug infusions as diagnostic tests to guide therapy, *e.g.*, intravenous phentolamine or epidural opioid, in most reports long-term treatment has been limited to responders to the infusion, which precludes validation of the infusion as a predictive test. In other clinical trials, drugs with selective actions have benefited too small a subset to yield a statistically significant result, but a second study of apparent responders, an "enriched enrollment" study,^{7,29,30} has confirmed that the subset responds consistently on repeated drug challenges.

Drug challenges have a potential advantage over sensory tests in that there are probably many more ways to stimulate or block sites of pain processing with selective drugs than with bedside examining tools. There are also limitations. A brief period of drug testing in the clinic may sometimes fail to predict how the patient will feel during the activities of daily life most limited by pain.⁸ Repeated exposures to drug make patients familiar with its side effects and increase the chance of "active placebo" effects.³¹

We suggest that regulators encourage the use of enriched enrollment studies in the development of treatments for chronic pain, including the possibility of accepting such data as evidence for efficacy when studies in broader populations are inconclusive. Of course, this will require greater attention to the methods for such studies. For example, we must learn more about how much analgesia might be produced if patients are unblinded by side effects, and what steps (active placebos, standard analgesic comparisons, blinding questionnaires) could minimize the chance of false-positive results.

Tissue Diagnosis as a Correlate of Pain Mechanism

Tissue type may provide a clue to mechanism because innervation pattern, mix of neurotransmitters, and central processing may differ among tissue types. This seems most compelling for pain resulting from damage to the nervous system, in which there are anatomic changes, such as sprouts from injured nerves, not seen in other persistent pain types. Galer *et al.*⁶ found that 58% of patients with a variety of peripheral nerve lesions reported excellent relief from a lidocaine infusion, compared with 21% of patients with lesions of other tissues. Tricyclic antidepressant drugs reduced pain in approximately 20 controlled clinical trials in patients with diabetic and other neuropathies, postherpetic neuralgia, and postmastectomy pain^{14,32} but have shown inconsistent effects in conditions of other tissues, including arthritis and idiopathic low back pain.^{33,34}

Although basic scientists have claimed that pain pro-

cessing in viscera may differ from other tissues (*e.g.*, transmission *via* dorsal column postsynaptic pathways³⁵ or response to peripheral κ opioids³⁶), there are too few clinical trials in visceral pain to examine tissue-related differences in analgesic response in humans. Nevertheless, there are indications that central sensitization may contribute to a secondary pain hypersensitivity in the gastrointestinal tract in a way that resembles secondary hyperalgesia in the skin.³⁷ Migraine, which may arise from afferent input from cerebral blood vessels and dura, has a sensitivity to drugs (the triptan 5-hydroxytryptamine 1D-E agonists) that are ineffective for other acute pains, implying a unique role for this receptor subtype in the pathogenesis of this particular pain, but it does respond to nonsteroidal antiinflammatory drugs and opioids, which have action on most nonneuropathic pains.

Disease Diagnosis as a Correlate of Pain Mechanism

Although traditional disease or syndrome diagnoses certainly encompass a mix of pain mechanisms, the differing tissue changes and time course in each diagnosis may make the mix of pain mechanisms different between disease groups. For example, although diabetic neuropathy and postherpetic neuralgia have resembled each other in their responses to tricyclic antidepressants and gabapentin, studies with the NMDA glutamate receptor antagonist dextromethorphan³⁸ have shown response in diabetics but not postherpetics. Compared with diabetic neuropathy, pain in human immunodeficiency virus-related neuropathy has appeared to be relatively resistant to amitriptyline^{39,40} but sensitive to nerve growth factor.⁴¹ Although some researchers have suggested that combining patients with mechanical allodynia across diagnostic groups would be a step toward mechanism-based diagnosis, it might even be more difficult to detect an effect in the combined group. As previously discussed, multiple mechanisms can give rise to allodynia, and different diagnostic groups might have different mixes of mechanisms.

Another example of disease diagnosis making a difference within a tissue category is the contrast in drug response between muscle strains and fibromyalgia. Muscle strains respond to the same antiinflammatory drugs, as do postoperative pain conditions. Fibromyalgia does not respond to antiinflammatory drugs⁴² but, unlike postoperative pain, is sensitive to tricyclic antidepressants.⁴³

A major obstacle to understanding the correlation of disease and tissue diagnosis with analgesic response is the virtual confinement of analgesic clinical trials to a few diseases, postoperative pain, neuropathic pain, headache, facial pain, arthritis, and cancer.⁴⁴ With their eyes on short-term costs and returns, industry scientists are reluctant to conduct clinical trials in a condition until academic investigators have demonstrated their feasibility. For this reason, we cannot yet answer the simple

question of whether results in the postoperative dental model predict usefulness in many of the most common chronic pain conditions.

Direct Comparisons of Analgesics Are Essential for Clinical Decisions

Mechanism-based diagnosis, whether based on symptoms, drug challenge, disease, or tissue, will better assist treatment if these criteria can be examined in studies that compare several different classes of analgesics. Granting agencies and regulatory guidelines should promote these types of comparisons, even when the comparator has not been approved for pain indications (*e.g.*, tricyclic antidepressants or gabapentin).

Testing Multiple Predictors of Response Will Require Large Sample Sizes and Improvements in Study Efficiency

It is likely that clinical researchers will identify some treatments that produce powerful and selective effects in some mechanistic subgroups, much like carbamazepine appears to have a particularly robust effect in classic trigeminal neuralgia. For many other analgesic agents, however, differences in response between diagnostic groups or between treatments will be small because of overlapping sets of mechanisms. Large sample sizes will be needed to show these differences, because sample size quadruples when one halves the size of the treatment difference one wishes to detect. Moreover, we have suggested that investigators examine many different clinical features—symptoms, sensory examination, drug response, disease, and tissue type—on drug response. The many simultaneous diagnostic groups being examined will also inflate the number of false-positive results occurring by chance. A convincing result will require even further increases of sample size or equivalent decreases in the variance. The large sample sizes will require multicenter trials (in which sophisticated quantitative sensory testing will be impractical) and put a premium on methodologic improvements to decrease the variance. Crossover trials, for example, appear to offer equivalent power to parallel-group studies that recruit 5–10 times the number of patients.⁴⁵ Regulatory agencies have been reluctant to accept data from crossover studies because they like to see a large number of patients treated anyway, and because statisticians criticized some crossover designs (particularly the two-period, two-treatment design) for vulnerability to carryover effects. Some statisticians consider these technical problems to be overstated,⁴⁶ but even if regulatory agencies continue to use only first-period data for pivotal demonstration of efficacy, they should encourage the use of

data from crossover periods to provide clues to individualizing treatment and comparing therapies.

In addition, pain researchers must take up the rarely addressed issue of which pain assessment techniques are most efficient in detecting treatment differences in chronic pain studies.⁴⁷ Small improvements in method could provide great gains. For example, Jensen and McFarland⁴⁸ suggested that averaging 7–14 diary ratings of pain over 1 week instead of using a single rating might eliminate as much as half the variance, an improvement equivalent to doubling the sample size.

Clinical Trial Data Describing Patient-by-Patient Diagnostic Features and Responses of Symptoms Must Be Made Widely Available

Many published analgesic trial reports often focus on mean outcomes of global pain rating scales. For example, two recent reports of large placebo-controlled studies of gabapentin in diabetic neuropathy¹⁵ and postherpetic neuralgia⁴⁹ showed statistically significant effects on overall pain and quality of life, but said nothing about response of the individual pain qualities that had been collected with tools such as the Short-Form McGill Pain Questionnaire or physical examination characteristics such as allodynia.

Investigators who discern patterns of response according to symptom or tissue or pharmacologic diagnosis in their own studies need to be able to reexamine individual patient data in other studies to confirm their hypotheses. However, even when investigators submit such large tables for publication, space limitation often makes this impossible. We propose that mechanisms be developed to encourage routine submission of detailed single-patient data and its storage in an easily accessed form such as a web site.

Can Tests of Clinical Pain Mechanisms Keep Up with Basic Science Insights?

Although pain clinicians have dreamed of being able to examine a patient and infer pain mechanisms, the ability of neurobiologists to dissect pain mechanisms in animals has created more possibilities than the clinician can currently distinguish using a standard history, a safety pin, von Frey hair, and thermal probe. Even with an expansion of the number of clinical researchers, this trend will probably continue. The most specific tools clinical researchers will have to dissect out pain mechanisms will be the new target- or mechanism-selective drugs. These would be used in combination with a more sophisticated history designed to elicit more information about possible mechanism and sensory or neurophysiologic tests.²⁷ For example, the importance of central sensitization might be assessed by response to NMDA

receptor antagonists. VR-1 receptor agonists and antagonists may be used to dissect the contribution of subpopulations of peripheral receptors and changes in their transduction. SNS or type III selective Na⁺ channel blockers, glutamate receptor subunit-specific antagonists, δ opiate receptor agonists, and adenosine subtype-selective agonists may also prove to be as important for diagnosis as for therapy.

Functional brain imaging may contribute to mechanistic inferences in intensive research settings, particularly if resolution improves enough to image small areas of the spinal cord and brainstem. Functional magnetic resonance and new positron emission tomography techniques make possible single-patient studies of the spatial and temporal patterns of functional change. Within a few years, knowledge of functionally significant polymorphisms in most human genes may facilitate new mechanistic distinctions within pain syndromes and help clinicians tailor treatments to address the abnormality in function.

Need for Collaboration among Research Sectors

A rational approach to mechanism-based treatment will require the validation of new assessment tools and diagnostic techniques, extension of pain research into the full range of common clinical pain conditions, and the collection and cross-analysis of data from large clinical trials. This is beyond the capacities of any sector of pain researchers. Academic researchers have the long-term perspective to explore underworked pain conditions and validate new tools, but their corresponding government research agencies fund few large analgesic trials. Industry already funds large trials but tends to want a shorter-term payoff and is leery of untested pain models or methods. Regulatory scientists often have seen the most data from new compounds and understand current research pitfalls but rarely have time or funding for research. Therefore, we propose a novel coordinated effort among these groups.

Recommendations

We recommend joint planning among research sectors. We encourage biomedical research funding agencies, drug regulatory agencies, industry, and academic scientists to develop novel collaborative mechanisms to hasten the impact of basic mechanistic insights on pain treatment and to that ensure lines of communication between basic scientists and clinicians are improved.

Biomedical research funding agencies should encourage research in the following areas:

1. comparison of data from animal models and clinical trials to optimize mechanism-based coordination be-

tween these two components of analgesic development;

2. development of more efficient methods for repeated-dose analgesic clinical trials, *e.g.*, determining which types of scales minimize variance;
3. development of valid assessment methods for multiple pain-related symptoms for large clinical trials, including pain qualities, and activity-evoked pain;
4. new tests to diagnose pain mechanisms, particularly those that can be extended to large multicenter clinical trials;
5. the strengths and weaknesses of short-term drug infusions as predictors of responses to chronic therapy;
6. development of clinical analgesic trials in common conditions rarely included in current research, particularly visceral pain syndromes related to the gastrointestinal, urinary, and reproductive organs and the heart; after groups of these patients are developed, a government-funded group of academic pain researchers might choose new compounds with interesting mechanisms to study in these populations, as a subsidized supplement to the few conditions studied in the usual industry analgesic development program;
7. head-to-head comparisons of several standard analgesics in common conditions where each drug has previously been compared only with placebo;
8. mechanisms of support for academic pain researchers to work alongside regulatory scientists to develop regulators' insights into confirmatory research.

Regulatory agencies should:

1. work with industry to understand the likely consequences of possible new methods of classifying pain and analgesic claims; it is essential that the collaboration outlined here not increase the cost of analgesic development; small companies have the most to gain from new niches, and their ideas should be considered;
2. encourage industry to incorporate new measures of subtypes of pain symptoms as routine secondary measures in their trials, and make fuller use of clinical trial methods well suited to detecting subgroup responses, such as crossover and enriched enrollment designs;
3. reward (with new types of permissible claims) companies' achievements in identifying and confirming new mechanism-based distinctions in pain symptoms and patient populations;
4. write new analgesic development guidelines, including a mechanism for frequent updates in collaboration with industry and academic scientists;
5. consider placing a greater emphasis on the inclusion of several types of active comparator drugs in phase 3 studies (after initial demonstration of efficacy).

The pharmaceutical industry should make individual data from all clinical trials available to the scientific

community in a manner that would not damage their competitive position. The professional pain-related organizations and their journals should encourage investigators submitting manuscripts to include tables of patient-by-patient data, including diagnostic features and response of distinct pain symptoms. In cases where this is too lengthy for print publication, an accessible web site should be provided.

In conclusion, based on an analysis of the potential utility of a mechanism-based approach to pain diagnosis, we make recommendations for a new concerted effort by academics, the pharmaceutical industry, and drug regulatory bodies to jointly introduce new tools to assess pain, validate these tools, and use them to improve the sensitivity and value of clinical pain trials.

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