Commentary

What can chronic arthritis pain teach about developing new analgesic drugs?

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Abstract

Chronic pain remains an important public health need with greater impact on the US economy than most other chronic conditions. Current pain management is largely limited to opioids and non-steroidal anti-inflammatory drugs, indicating a gap in the translation of new knowledge to the development of improved pain treatments. Strategies suggested include the re-evaluation of current drug screening methods, a recognition that molecular-genetic events occurring acutely contribute to the development of pain chronicity, the validation of analgesic targets in the intended patient population, consideration of the unique genetic profile that varies between individuals, and the introduction of individual response measures to improve the capture of outcomes in clinical trials.

Keywords: analgesics, chronic pain, drug development, individual responses, pain mechanisms

Despite the availability of opium and willow-bark derivatives for centuries, chronic pain remains an important unmet public health need. Although definitive epidemiologic data are lacking, millions of Americans [1] live with serious (malignant and non-malignant) chronic pain; this pain subsequently affects almost every aspect of their lives. In fact, a recent study suggests that chronic pain has a greater impact (about US$100 billion annually) on the US economy in health insurance, lost wages, and reduced productivity than any other chronic condition including heart disease, hypertension, and diabetes [2]. Unmet needs for analgesia are also recognized by the US Congress, which has declared 2000–10 to be 'The decade of pain management and research'. Although the recognition of pain as the 'fifth vital sign', continuing improvements in professional pain education, and the development of pain and palliative care services hold promise for improved pain therapy, these efforts are ultimately limited by the safety and efficacy of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and all their variations and formulations. It has therefore been argued that the apparent continuing failure to develop fundamentally new and different analgesic drugs contributes significantly to the unmet needs in chronic pain management [3]. This further suggests that there is a need for new strategies and new thinking regarding therapeutic targets for treating pain, both acute and chronic.

To rheumatologists, the statement that there are unmet clinical needs in chronic pain is probably not too surprising because they deal routinely with chronic pain in their patients with osteoarthritis (OA), a leading cause of chronic pain and disability in the USA estimated to affect nearly 21 million Americans [4]. Treating the chronic pain associated with OA alone costs millions of dollars in direct analgesic drug costs, as well as those costs necessary to deal with the inevitable adverse events (namely gastrointestinal bleeds) that these drugs also bring to the therapeutic table. Similarly, pain associated with other arthritic diseases such as rheumatoid arthritis (RA), which affects an estimated 1% of US adults, is another example of other causes of chronic pain in rheumatic diseases. Possibly even more familiar to rheumatologists today is the increasingly recognized condition called fibromyalgia that currently represents a substantial unmet need and clinical challenge for pain therapy. In fact, probably all rheumato-

MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis.

logic diseases can evoke pain at some point that is often poorly managed. Therefore, patients who frequent a rheumatologist in the clinic represent a substantial portion of the total US burden of chronic pain and also arguably present the spectrum of mechanisms that cause such pain.

Despite the sequencing of the human genome, the cloning of animals and the advent of clinically useful biological agents to treat a wide variety of diseases (especially rheumatic diseases), few truly new and widely effective molecular entities designed to treat pain mechanisms have entered the analgesic clinic in the past 10–20 years. Why, then, is there such a gap in the translation of new knowledge and technologies into different and better treatments for one of the oldest medical problems known to humans?

It is likely that the potential of genomics and proteomics will permit a better description of the molecular-genetic basis of acute and chronic inflammation. These new tools and thinking will also probably lead to a deeper understanding of the plasticity in the nervous system that is argued to be an important pathway to chronic pain that no longer depends on obvious peripheral causes. It is therefore likely that this new knowledge will lead to new targets for analgesia and new chemical entities entering the drug development pipeline of the future. However, existing clinical trial settings have the apparent limitation of only identifying drugs with mechanisms of action similar to already approved drugs, while screening out analgesics with completely new mechanisms of action, as these clinical models have usually been validated by demonstrating opioid or NSAID activity. This circular process therefore may fail to detect drugs acting through non-opioid or non-NSAID mechanisms because these investigational analgesics might never advance beyond the initial proof-of-concept studies. The high cost of drug development, now estimated at $800 million per new chemical entity [5], may further act as a deterrent to developing truly novel analgesics, because a failure would be too costly.

A recent workshop organized jointly by the National Institutes of Health and the US Food and Drug Administration [3] identified several methodologic issues that act as barriers toward the development of novel analgesic drugs. It was noted, for example, that most pain research conducted in the past 150 years has studied transient pain that does not result in tissue damage sufficient to have much relevance to clinical medicine as a model for chronic disease. The artificial temporal differentiation between acute (days to weeks) and chronic (months) pain may also be problematic because key pathophysiologic processes may diverge early in the development of pain chronicity. Chronic pain studies based on enrolling patients who have had pain for months might miss critical points for evaluating an intervention aimed at preventing or pre-empting the development of the chronic disorder and subsequent irreversible changes. This situation may be especially true for the contribution of peripheral and central sensitization to the transition from acute injury to chronic pain.

Conversely, traditional animal and clinical models employed to screen for analgesics might not be useful for studying the transition from acute injury to chronic pain if the critical events occur days after the injury when acute pain is usually resolving symptomatically. This limitation is even more important if these same pain models are not able to identify analgesics that have a fundamentally different mechanism of action from that of traditional NSAIDs or opioid-type drugs. This discrepancy is illustrated by the promise suggested for neurokinin-1 antagonists by animal-based studies and their failure to demonstrate analgesic activity in human clinical conditions [6]. This disconnect may also illustrate that currently available non-clinical animal models are not good surrogates for the clinical needs of chronic pain. Therefore, if non-clinical models that are sensitive to mechanisms other than anti-inflammatory effects cannot readily be developed, other alternatives in the clinical setting need to be explored.

A shift in the strategies used for analgesic drug development is called for by Woolf and colleagues [7]. They argue that understanding analgesic mechanisms provides an opportunity to move forward by assessing the effects of investigational analgesics on the mechanisms involved rather than the empirical method that has driven analgesic development in the past. The symptoms that comprise the pain experience are the result of specific and identifiable changes in the nervous system. Analgesics, Woolf argues, do not have intrinsic pain-relieving actions; rather, they produce their effects because they interfere with the mechanisms that produce the pain. Analgesia will not occur if the particular mechanism that a drug interacts with is not present in the patient. Conversely, if a patient has a pathophysiologic process that is driving their pain, that mechanism should be the target of action of the analgesic. This extends to the clinical differences between acute and chronic pain; they are not distinct states of the nervous system. Acute pain refers to pain at certain times after initiating events that may be transient; chronic pain refers to the persistence of the mechanisms activated by the tissue injury. The way to move forward clinically is to measure multiple signs and symptoms, not just global measures such as patient report of pain, and to validate hypotheses about the mechanisms that convert a short-lasting pain into a pain that persists and becomes intractable rather than returning to baseline.

Pharmacogenomics is another possible strategy for enhancing analgesic drug development and pain therapy. It

rests on the ability to relate the responses of an individual to a drug regimen to some aspect of their genetic composition. If demonstrated in a sufficient number of individuals, it might be possible to derive a causal relationship between specific genetic polymorphisms and therapeutic response. If one's genetic profile influences one's molecular pathways for pain and response to an analgesic in terms of efficacy or safety, these important factors may revolve around the unique individual.

Properly constructed individual response measures hold the potential to improve the capture of clinical outcomes in clinical trials; more so than approaching the same problem from a group or means perspective (RA Dionne, L Bartoshuk, J Mogil and J Witter, unpublished work). Validating the role of an individual responder approach for clinical analgesic trials will better capture clinically important outcomes in clinical trials, possibly leading to the identification of subgroups of patients whose underlying molecular-genetic pain mechanism provides a favorable therapeutic ratio for an analgesic drug.

Therefore, in thinking about the transition from acute pain after tissue injury to chronic pain sustained in the absence of damage, one can then ask the following types of question: How much of chronic pain is caused by mechanisms that are initiated by acute pain processes in the periphery, for example inflammation; by reactive processes in the central nervous system, for example sensitization due to the release of excitatory amino acids; and by the continuing disease process, for example RA or OA? Should drug selection for these distinct processes vary to target the acute inflammatory response, the transition to chronicity, or the underlying disease process to minimize continued destructive changes despite successful symptom management? Should pivotal clinical trials for screening and confirming investigational drugs continue to be based on clinical models that have been validated with the use of existing drug classes (NSAIDs, opioids), or will scientific advances translate more successfully into improved pain therapy by the development of new approaches to clinical evaluation of putative analgesic drugs?

Both the drug methotrexate (MTX) and the biologic agent etanercept are examples of therapies widely employed to treat rheumatoid arthritis. The evidence to support such use comes from clinical trials that have used the American College of Rheumatology (ACR) 20 responder analysis as the endpoint. Pain relief is the primary goal of any therapy in RA, and the ACR 20 employs pain (100 mm visual analog scale) as one of its endpoints. Because the response to MTX generally takes days to weeks to become apparent, it is not surprising that there is no information available in the literature to suggest that MTX would be useful to treat acute pain. This would therefore suggest that whatever mechanisms underlie how MTX improves pain in RA are different from those that cause pain in an acute situation. In contrast, the pain relief associated with the use of etanercept has been described as rapid and dramatic, suggesting that the tumor necrosis factor pathway has an equally important role in chronic pain and the other processes associated with chronic inflammation. It is noteworthy that neither MTX nor etanercept has found use in the chronic pain associated with fibromyalgia. It is therefore unknown how these two arthritic therapies differ in their ability to interfere with the underlying disease processes that contribute to nociceptive processes versus the symptom complex called pain as experienced in the somatosensory cortex. Furthermore, it is likely that neither agent would have survived for long in a traditional analgesic development program with a 'pivotal' clinical trial in an acute anti-inflammatory model such as oral surgery or bunion surgery.

So perhaps a reconsideration of acute versus chronic pain, and acute versus chronic inflammation, might be useful as we move forward in this 'Decade of pain management and research'. A better understanding of the relationships that exist mechanistically in acute versus chronic pain might allow the development of new therapies that will optimize the treatment of pain. Acute pain that is treated from an understanding of both a mechanistic and clinical perspective may lower the probability that such acute pain might ultimately contribute to chronic pain. Chronic pain that is treated from an understanding of its mechanistic and clinical perspectives might then be pain that is ultimately cured.

Competing interests

The author(s) declare that they have no competing interests.

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