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TRANSLATIONAL PAIN RESEARCH: ACHIEVEMENTS AND CHALLENGES

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Abstract

The achievements in both preclinical and clinical pain research over the past four decades have led to significant progresses in clinical pain management. However, pain research still faces enormous challenges and there remain many obstacles in the treatment of clinical pain, particularly chronic pain. Translational pain research needs to involve a number of important areas including a) bridging the gap between pain research and clinical pain management, b) developing objective pain assessment tools, c) analyzing current theories of pain mechanisms and their relevance to clinical pain, d) exploring new tools for both preclinical and clinical pain research, and e) coordinating research efforts among basic scientists, clinical investigators, and pain medicine practitioners. These issues are discussed in this article in light of the achievements and challenges of translational pain research.

Introduction

Pain medicine is one of few medical specialties that rely heavily on individual self-reporting to make a clinical diagnosis. Although modern diagnostic tools are available to assess pathological conditions, pain is historically considered as a subjective experience that has enormous individual variation. Indeed, current pain management strategies, especially for chronic pain, are based largely on empirical approaches that are insufficient due to a number of clinical challenges including a) mismatch between subjective pain complaint and pathological condition, b) individual variation and multidimensional features of pain, and c) clinical challenges and confounding factors.

Mismatch between pain complaint and pathological condition

In the clinical setting, an individual's self-reporting of pain often does not correlate well with the severity of pathological condition because a) pain can result from seemingly trivial tissue damage (e.g., Complex Regional Pain Syndrome Type I), b) duration of chronic pain often outlasts that of the original insult, c) there may be an over-focus on common causes of clinical pain and there exists limited knowledge on the underlying mechanisms of many clinical pain conditions, and d) transition from acute to chronic pain may be associated with changes in the brain morphology and influenced by an individual's genetic predisposition [3, 31, 103].

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Individual variation and multi-dimensional features of pain

Pain is highly individualized with respect to the intensity, quality, and clinical comorbidity such as depression and post-traumatic stress disorder [16, 86, 103]. Moreover, a painful experience has multi-dimensions including sensory discriminative, cognitive, autonomic and affective responses and has gender and cultural differences [15, 25, 51, 96]. To date, no single clinical tool captures all dimensions of pain objectively, causing undertreatment of pain in some cases and inappropriate treatment in others.

Clinical challenges and confounding factors

For example, patients with fibromyalgia often complain of pain at multiple body sites with accompanying depression and personal distress. Pain medicine practitioners often have to make empirical choices from various treatment modalities such as interventional procedures (e.g., nerve block), analgesics, antidepressants, anxiolytics, psychological coping, and social support. In many cases, formulating an effective treatment plan becomes a process of repeated trials and errors, frustrating both patients and clinical practitioners. Moreover, issues related to potential secondary gains (e.g., lawsuit over motor vehicle accident or dispute over work-related injury) and unwanted consequences from medications (e.g., addiction to opioid analgesics) challenge the clinical validity of self-reporting of pain as both a diagnostic and prognostic tool.

Given these unique challenges of clinical pain, translational pain research has emerged as an important field that promotes coordinated bi-directional research approaches between bedside and bench in order to bridge the gap between pain research and clinical pain management. Translational pain research needs to make real progresses in several major areas including a) understanding limitations of current preclinical and clinical pain research, b) developing objective and clinically meaningful pain assessment tools, and c) planning long-term strategies and exploring new research tools to guide both preclinical and clinical pain research. These issues will be discussed in this article in the context of the achievements and challenges of translational pain research.

What have been translated over decades?

The achievements in preclinical and clinical pain research over the past four decades have led to significant progresses in clinical pain management. These achievements may be summarized in four general areas: a) theories of pain mechanisms, b) new additions in the armamentarium of pain medications, c) new modalities of interventional pain management, and d) potential targets for new drug development.

Prior and current theories of pain mechanisms

Contemporary pain research has been inspired by prior and current theories of pain mechanisms such as Gate Control Theory [18, 55, 56, 80, 81, 84, 87, 94, 98]. Over years, the concept of neuroplasticity that the nervous system responds to tissue damage with active changes has stimulated extensive research to understand the cellular and molecular mechanisms of peripheral and central sensitization [5, 6, 17, 19, 20, 24, 36, 37, 43, 62, 78, 97, 104, 132, 135, 138, 141, 146]. Investigations into new pain mechanisms have indeed played a vital role in guiding innovative translational efforts in pain medicine. For instance, evidence for ectopic discharges at the dorsal root ganglion after nerve injury [30] and the discovery of new sodium channel subtypes [95] led to clinical trials of various sodium channel blockers and the introduction of a clinical intravenous lidocaine test [71]. Similarly, new findings from an ever growing number of signal transduction pathways contributory to peripheral and central sensitization have resulted in many attempts of new drug development targeting the nociceptive pathways at the transcriptional, translational, and/or post-translational level [33, 34, 54, 66, 75, 77, 92, 93, 95, 116,

[117, 119, 127, 128, 130, 134, 138, 140, 142, 143]. An important aspect of contemporary pain research is that pain is no longer considered to be a passive response of tissue damage but an active process that involves plastic changes at both the system and cellular level, although how these plastic changes contribute to hyperalgesia or allodynia in the clinical setting remains largely unclear.

New additions in clinical pain management

There have been many important improvements in clinical pain management including new tools in acute pain treatment, new drug delivery systems, and a few new pain medications.

1. Clinical management of acute pain including postoperative pain has been dramatically improved. For example, patient-controlled analgesia (PCA), either intravenous or epidural, has provided an effective tool to manage postoperative pain. Introducing PCA into daily clinical practice would not have been possible without extensive preclinical and clinical research on the pharmacology of systemic and spinal analgesics [9, 63, 111, 139, 140, 141]. By comparison, clinical management of chronic pain remains difficult, particularly pathological pain such as that from injury to the nervous system.

2. Perhaps the most notable advancement in pain medicine are those emerging new drug delivery systems that have extended the use of analgesics beyond conventional (e.g., oral, intravenous, intramuscular) drug delivery routes. As listed in Table 1, new drug delivery systems include, but are not limited to, transdermal, transmucosal, topical, intranasal, and neuraxial (intrathecal/epidural) administration of opioid analgesics, local anesthetics, and non-steroidal anti-inflammatory drugs [9, 27, 28, 50, 63, 89, 109, 111, 112, 114, 139, 140, 141]. In many cases, these new drug delivery systems provide more comfort for patients, fewer side effects, and a quicker onset of pain relief than conventional drug delivery methods. In addition, new drug formulae such as extended versus immediate release opioid analgesics allow clinicians to tailor the pain treatment for various clinical pain patterns (e.g., constant versus episodic) with different drug combinations. These new drug delivery systems are invented to meet clinical needs, which is inspired by the better understanding of pain mechanisms through preclinical and clinical research.

3. The list of pain medications currently in clinical use has been expanded, when compared to that of several decades ago (Table 1). New additions in the armamentarium of pain medications may be divided into three groups. (a) Most of these new additions are those medications already in use for other clinical conditions including broad (e.g., tricyclic antidepressants) or selective serotonin and/or norepinephrine reuptake inhibitors and central-acting alpha2 adrenoreceptor agonists [68, 108]. Additional examples include anticonvulsants such as gabapentin, which were initially developed for the seizure treatment and now widely used for pain management [72]. (b) There is a significant expansion of opioid analgesics along with innovative drug delivery systems [9, 27, 63, 111, 112, 114, 139, 140, 141, 139]. (c) Only a few new agents have been brought into clinical practice, including cyclooxygenase-2 (COX-2) inhibitors (anti-inflammatory drugs), triptans (anti-migraine agents), tramadol (an analgesic with mixed mechanisms of action), and selective calcium channel blocker [2, 29, 46, 61, 125]. Unfortunately, the majority of these new agents have only limited clinical utility due to their adverse effects such as cardiovascular side effects (e.g., COX-2 inhibitors) and neurotoxicity (e.g., selective calcium channel blocker) [2, 12, 83].

New modalities of interventional pain management

Innovation in new medical technologies has led to a substantial improvement in interventional pain management. While the extent of their clinical utility is debatable, interventional procedures (e.g., epidural steroid injection) are undoubtedly an integral part of contemporary pain medicine. Several new modalities of interventional procedures, including sympathetic block, spinal cord stimulation, and implanted intrathecal pump for spinal drug delivery, become available owing to the success in preclinical and clinical pain research. Recently, deep brain stimulation, commonly used to treat motor disorders, has been tried as a possible clinical tool for managing intractable neuropathic pain [121].

Potential targets for new drug development

Despite few success stories, extensive efforts are being made for new drug development. The readers are directed to the references cited in Table 2 with regard to more than a dozen potential targets of new drug development. These potential targets are identified through preclinical research, some of which have gone through extensive clinical trials. In general, many of these pipeline drugs need to clear huge hurdles such as their small therapeutic window and severe adverse effects. Moreover, many of these potential drugs target redundant cellular sites (e.g., receptors and kinases within a cellular cascade) of the nociceptive pathways, which often lack the specificity (nociception specific) at both the cellular and system level.

The scope of translational pain research

Despite the above-mentioned achievements, pain research still faces enormous challenges and there remain many obstacles in the treatment of clinical pain, particularly chronic pain. There clearly is an urgent need for clinically meaningful translational pain research [22, 69]. Traditionally, translational research is regarded as a process of bringing bench findings to clinical application. Translational pain research, however, will require coordinated bi-directional approaches between bedside and bench because of the subjective nature of pain experiences.

Translational pain research needs to involve the following areas. (1) Current theories or concepts of pain mechanisms need to be critically reviewed and analyzed to provide a new roadmap of contemporary pain research. Preclinical research should move beyond studying the mechanisms of nociception to include investigations into the brain processing of pain perception and its related motor, autonomic and psychological responses. For instance, it would be of significance to compare the similarities and differences in the cellular process between the spinal cord and various brain regions in response to peripheral nociceptive input. (2) Differences and similarities between animal and human experimental pain models and their relationship with clinical pain conditions should be compared and the limitations of these models are appropriately recognized. Experimental “pain” models, particularly preclinical models, are the foundation of pain research. Their relevance to clinical pain should be constantly revisited. (3) Limitations of preclinical and clinical pain assessment tools have been well recognized. As such, developing innovative objective pain assessment and monitoring tools should be a top priority of translational pain research. (4) Current strategies of new drug development need to be evaluated and perhaps overhauled. Specific considerations should be given to understand the limitation of pharmacological interventions targeting similar cellular and intracellular mechanisms that may or may not be specific to the processing of nociception and pain. (5) Dialogues between researchers and clinical practitioners must be strengthened as an important part of translational pain research. Some of these issues will be further discussed in the remaining of this article.

Recognizing the gap between current pain mechanisms and clinical pain

For decades, preclinical research has focused on the cellular and molecular mechanisms of peripheral and central sensitization induced by tissue damage. Although overwhelming evidence supports the notion that neuroplasticity in the form of cellular and molecular changes occurs at both peripheral and central loci after tissue damage (see above references), it is unclear whether the concept of neuroplasticity is sufficient to explain the chronicity and diversity of clinical pain phenomenon.

1. Pathological pain can result from trivial tissue damage [e.g., complex regional pain syndrome (CRPS) type I] and often lasts far beyond the duration of the original impact [38, 99, 103]. How does trivial tissue damage produce lasting neuroplastic changes leading to persistent clinical pain? What are the mechanisms underlying the transition from acute to chronic pain? If neuroplasticity is a collective outcome of many initial changes after tissue damage, how does neuroplasticity become sustained at months and years after the initial injury?

2. The intensity of clinical pain such as CRPS is comparable with that of physiological (experimental) pain (e.g., response to transient heat stimulation) [100, 103]. That is, pathological pain (e.g., following peripheral nerve injury) is not necessarily more painful than physiological pain if judged by pain intensity alone. By contrast, words used to describe pathological pain (e.g., burning, nagging, diffuse, debilitating) indicate changes in pain quality as well as emotional and affective pain responses [79]. If so, what is the biological basis of such differences between physiological and pathological pain? A relationship has yet to be established between biochemical and molecular changes (often being focused at the spinal level) after tissue damage and a persistent clinical pain state that reflects more on changes in pain perception than the nociceptive processing.

3. Clinical pain is often characterized as spontaneous pain, which refers to the type of pain that occurs in the absence of overt peripheral stimulation [16, 103]. Moreover, clinical pain is highly dynamic in the intensity, timing, duration, location, quality, and sensory modality. Patients often describe their chronic pain as having ‘good days and bad days’. In many cases, allodynia can become hyperalgesia, and *vise versa*, in the same affected skin area [38, 99, 103]. If so, does the concept of neuroplastic changes after tissue damage adequately predict and explain such diversities of clinical pain patterns?

4. An intriguing hypothesis based on the concept of neuroplasticity and central sensitization is the idea of preemptive analgesia [26, 58, 137]. A considerable number of clinical studies have been conducted to test this hypothesis and the outcome has been inconsistent [69, 113, 144]. By comparison, most preclinical studies report effective treatments from comparable doses of the same test compounds. Where does this gap come from? Is the preclinical information lost in translation or is there a deficiency in the conceptual framework that guides these clinical studies? More discussion on these issues will be provided below.

Translational pain research can make major differences by providing timely and critical feedbacks to both researchers and clinicians, through critically analyzing current theories of pain mechanisms and research approaches. A system, similar to that used to assess the validity of clinical trials, should be established to examine the relevance of preclinical research to clinical pain. This system should also track the success and failure of translational efforts such as clinical trials and provide the post-market analysis of any new pain medication or treatment modality. To this end, translational pain research could function as a “think tank” to 1) avoid the behavior of “cluster research” that leads to repetitive research themes and 2) guide clinical

research before a major drug development effort is launched through costly and far too often disappointing clinical trials.

Issues related to translation from bedside to bench

The subjective nature of pain experiences makes it difficult, if not impossible, to produce experimental "pain" in animals. Indeed, mimicking clinical pain conditions using animal models is the most challenging first step of translational pain research. Several issues are worthwhile considering.

Experimental "pain" models

Arguably, animal 'pain' models only produce conditions of tissue damage (nociception) but not necessarily all dimensions of clinical pain (a subjective experience). Even if animal models do duplicate clinical pain experiences like humans, there is a lack of effective assessment tools (e.g., a well-designed operant assessment paradigm) to detect different dimensions of pain experiences in animals. Therefore, the successful intervention of nociception demonstrated in animal models may or may not predict a similar outcome for clinical pain, because animal models of tissue damage (e.g., nerve injury) do not necessarily duplicate multi-dimensions of clinical pain. Although in many cases blocking nociception is a necessary step in clinical pain management, it is often not a sufficient step for the treatment of many chronic pain conditions. In this regard, a distinction between pain and nociception must be clearly made in preclinical and clinical research, as it is not just a semantic issue. The deficiency of animal 'pain' models makes the translation from bench to bedside rather unpredictable. A step in the right direction would be to include those assessment parameters that may reflect the perception of nociception in experimental animals, such as spontaneous pain behaviors and operant pain paradigms [73, 85].

Spontaneous versus stimulus-induced pain

Spontaneous pain is a salient feature of clinical pain. But, is this type of clinical pain really spontaneous? What is the generator of spontaneous pain, especially for those pain conditions (e.g., CRPS type I) that appear to be absent of overt tissue injury? Does testing the nociceptive response (e.g., stimulus-evoked response) in animal models capture this important feature of clinical pain? Observation of spontaneous pain behaviors and operant pain assessment paradigms are not commonly used in preclinical research, presumably because these methods are time-consuming and difficult to quantify and the results are just as difficult to interpret. After all, if clinicians could not validate whether a patient is indeed having pain, how could one tell what a rodent is feeling about nociception? However, those behavioral tests that almost exclusively focus on stimulus-induced responses do deepen the deficiency in preclinical pain research and complicate the translation from bench to bedside. For example, despite the fact that thermal hyperalgesia is hardly a clinical issue, testing thermal hyperalgesia is the most commonly used behavioral endpoint in preclinical research. As such, those pharmacological interventions that appear to be effective in preventing or reversing thermal hyperalgesia in animal "pain" models are often prematurely and perhaps erroneously used to launch a multi-million dollar new drug development program. If so, one might also wonder whether a strategy of new drug development aimed at blocking thermal hyperalgesia alone using TRPV1 antagonists would have a broad clinical implication.

Acute versus chronic (pathological) pain

One of the examples of acute pain is uncomplicated and temporary postoperative pain. In many cases, acute pain can be effectively managed with analgesics (e.g., epidural, oral or intravenous). By contrast, pathological pain such as neuropathic pain (e.g., post-herpetic neuralgia, CRPS I or CRPS II) often presents a prolonged time course and remains very difficult

to treat. Over years, preclinical research has focused on these immediate (within days or weeks) cellular and molecular changes following nerve injury. Are these changes in *nociceptive* responses truly responsible for a persistent *pain* state that is present at weeks, months or even years after the initial injury? That is, is the initiating nociceptive barrage sufficient to trigger a long-lasting pain state or is a persistent, low-level nociceptor discharge required to sustain these changes? Is chronic pain a continuum of a prolonged acute nociceptive state or a result of recurrent acute pain (e.g., chronic lower back pain due to repeated lumbar disk herniation)? Translational research should be positioned to explore the relationship between these initial responses to tissue damage and a chronic pain state that is more likely to involve changes in the perception of nociception.

Constructive dialogue in the field

Translational pain research requires constructive dialogues among basic scientists, pain practitioners, pharmaceutical chemists, and patients as well as collaborations among various clinical disciplines including anesthesiology/pain medicine, orthopedic surgery and neurosurgery, physical medicine and rehabilitation, neurology, rheumatology, palliative care, oncology, psychology, and psychiatry/addiction medicine. To date, only a few academic institutions have launched translational pain research programs, many of which are focused on promoting clinical trials. Clearly, more efforts need to be made to facilitate such dialogues.

Issues related to translation from bench to bedside

A failed clinical trial could be due to the flawed (conceptual or technical) preclinical information, a poor clinical study design, and/or the reality that human biology differs from that of non-humans. If clinical trials fail because the bench information is lost in the process of translation, what factors may turn a potentially successful clinical trial into a failed one? The following text will use N-methyl-D-aspartate (NMDA) receptor antagonists as an example to discuss several common issues related to this topic.

Preclinical research strongly supports a critical role of the NMDA receptor in the mechanisms of pathological pain, because investigational (AP-5, MK-801) or clinically available (ketamine, amantadine) NMDA receptor antagonists have been repeatedly shown to be effective in preventing or reversing hyperalgesia in animal models of inflammation or nerve injury [21, 32, 35, 74, 137]. These reproducible preclinical findings have led to a large number of clinical studies (both randomized studies and case observations) to examine the clinical utility of NMDA receptor antagonists [113]. However, clinical outcomes from these studies are substantially inconsistent (see selected examples in Table 3). Besides the lack of selective NMDA receptor antagonists, the following issues may have contributed to the discrepancy between the preclinical and clinical findings.

Experimental conditions

Preclinical studies demonstrate that NMDA receptors play a pivotal role in the mechanisms of central sensitization [35, 74, 122]. In general, preclinical studies consistently show that NMDA receptors are not involved in physiological “pain” such as that following transient noxious stimulation without persistent tissue damage because blocking NMDA receptors does not change the baseline nociceptive response to nociceptive stimulation [70]. If so, NMDA receptor antagonists would be expected to reduce hyperalgesia (returning the nociceptive threshold to the baseline) but not to produce analgesia (raising the nociceptive threshold above the baseline). With this in mind, those positive versus negative clinical studies listed in Table 3 appear to be largely correspondent to the etiology of pain conditions in these clinical studies. Negative outcome studies are often associated with acute postoperative pain conditions whereas positive outcome studies with neuropathic pain conditions (e.g., hyperalgesia). Therefore, a meaningful

translation process through clinical studies should begin with careful choices of appropriate clinical pain conditions that are consistent with the conditions examined in preclinical models.

Pharmacokinetic and pharmacodynamic issues

A detailed discussion on the role of pharmacokinetic (PK) and pharmacodynamic (PD) issues in translational research is beyond the scope of this article. However, differences in dose regimens (e.g., half-life, bioavailability) between animal and human studies may be a critical contributing factor to the outcome of a clinical study. For example, animal studies suggest that tonic activation of NMDA receptors after tissue injury is initiated and maintained by peripheral nociceptive input [49]. As such, the continuous presence of an NMDA receptor antagonist is required to block the development of hyperalgesia in animal models [73, 105]. As shown in Table 3, those negative outcome studies often used a single dose regimen whereas a multi-dose regimen was used in these positive outcome studies. In some cases, the doses for an agent used in animal studies may not be achievable in human studies due to side effects. Therefore, a potential mismatch in the PK/PD issues between animal and human studies should be carefully considered in designing clinical studies in order to identify the critical period of potential contributions to clinical pain conditions from a certain cellular response (e.g., activation of NMDA receptors).

Pain assessment tools

A withdrawal response to thermal or mechanical stimulation is the most commonly used preclinical tool to assess nociceptive behavior, whereas a self-reporting system (visual analog or numerical pain scales) is used to assess pain in clinical studies. This mismatch has significant implications in translational research because different assessment tools evaluate different aspects of a pain condition. A stimulus-based withdrawal response primarily reflects a spinally mediated process of nociception, whereas a self-reporting system provides information of pain experiences (the perception of nociception that must involve the brain). Neither a withdrawal response nor a self-reporting system is optimal for the pain assessment. However, when two different assessment tools are used in preclinical versus clinical studies, two very different study endpoints requiring different neural structures and processes are being compared, multiplying the unpredictability of clinical studies.

Comorbidity, gender and genetic difference, and secondary gains

Chronic pain often exists with clinical comorbidity such as depression and is confounded by many clinical factors (e.g., issues related to secondary gains). A recent study shows that mechanical allodynia is exacerbated in rats with depressive behaviors [145], suggesting that comorbidity could influence nociception and its behavioral assessment in animal studies as well. Moreover, most preclinical studies do not take into consideration the gender difference whereas clinical data clearly show differences in pain perception between male and female subjects [123]. There are also concerns regarding the pharmacogenetic influence on clinical responses to a drug therapy [44]. If clinical trials are conducted under a “pure” clinical condition (a limited age range, gender selection, lack of comorbidity, a selective range of pain scores), how could a new drug be expected to help pain patients who happen to be outside the 95% limit of inclusion criteria of such clinical trials? A related issue is that placebo responders and non-responders could further confound the clinical trial outcome, which leads to the next topic on searching for objective clinical pain assessment tools.

Searching for objective pain assessment tools

The lack of objective clinical pain assessment tools makes it difficult to conduct clinical studies, provide valid clinical diagnosis, and adequately evaluate treatment outcomes. Therefore, searching for objective pain assessment tools is a fundamentally important challenge of pain

research. To date, clinical pain assessment tools remain subjective and unreliable. Due to the scope of this article, only a brief discussion is provided for each assessment tool in the following text.

Self-reporting of pain

Currently, this is the only tool used to assess clinical pain conditions. Patients report pain intensity (sometimes pain affect as well) on a numerical or visual analog scale (e.g., 0–10) or through identifying facial or other drawings. These systems are obviously subjective with enormous individual variations [39]. Recently, the Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) declared pain as a fifth vital sign (as opposed to a symptom). While other vital signs (heart rate, blood pressure, temperature, and respiration rate) are objectively measurable, pain is measured in subjective terms (i.e., pain score). Another problem with self-reporting systems is that they are seldom given an anchor or reference point for the scale, if such an anchor or reference point can be practically established. As such, self-reporting systems may be useful for within-subject comparisons (e.g., before or after a treatment) but woefully inadequate for between-subject comparisons.

Quantitative sensory testing (QST)

QST is mainly used in clinical pain research to examine pain threshold and tolerance in response to a calibrated stimulus (e.g., thermal stimulation at 43 °C vs. 46 °C), which somewhat mimics behavioral testing in animal studies. Although the stimulus intensity is quantitative, the response to stimulation is still reported in a subjective term. Moreover, such responses do not adequately differentiate between the intensity and affective dimension of pain.

Sympathetically mediated response

This method detects changes in sympathetically mediated responses to pain such as changes in heart rate and skin impedance [118]. However, the information obtained using this technique captures only secondary responses to pain but not pain perception *per se*. This method is also subject to confounding factors (e.g., anxiety) and its sensitivity and specificity are clearly diminished in chronic pain conditions.

Neuroimaging

Neuroimaging methods, such as fMRI and PET, have provided significant information on the brain processing of pain [3, 7, 25, 96, 120] and proposed to be used to aid clinical diagnosis of pain (as pain markers) and new drug development [11, 22]. Technically, fMRI and PET images do not provide the real-time dynamic response of pain; whereas electroencephalography (EEG) alone has limited spatial resolution. Other neurophysiological tools such as magnetoencephalography in combination with anatomic MRI or fMRI as well as biomarkers for nociception may be better situated to obtain both temporal and spatial information of clinical pain [102].

Biomarkers and genetic information

Can biological markers such as the waxing and waning of a cellular element (e.g., cytokine) and/or genetic information be used as objective indicators of clinical pain? Can such markers be used to predict transitions from acute to chronic pain? Research in this area has just begun and more information will become available, although it appears unlikely that either biological markers or genetic information alone would be sufficient to diagnose or predict a clinical pain condition. Steps need to be taken to differentiate these markers as “by-standers” and “causal players” in the mechanisms of pathological pain. Moreover, a critical distinction needs to be made between biomarkers for nociception after tissue damage (e.g., change in proinflammatory

cytokines) and potential markers for clinical pain experiences (e.g., cortical neurophysiological responses).

Mechanism-based pain phenotyping

A decade ago, a group of scientists in the pain field proposed to link clinical pain to the underlying cellular mechanisms (i.e., mechanism-based pain classification) and to use this approach to improving clinical pain treatment [136]. Although this concept has its merit, the clinical reality remains far removed from this tantalizing idea for several reasons: a) multiple cellular mechanisms are often responsible for a single clinical pain phenotype, b) multiple clinical pain phenotypes often dynamically present in a same patient, c) currently available pain medications are hardly specific for any particular cellular mechanism, and d) there is a lack of objective pain assessment tool to evaluate the effectiveness, or lack thereof, of a given treatment regimen.

In summary, searching for objective pain assessment tools should be considered as one of the top priorities of translational pain research. Indeed, the above discussion raises more questions than solutions, but the need for strengthening this research area is well recognized. The success in this area will help a) reform current empirical clinical pain management approaches, b) revolutionize clinical and basic science pain research, c) formulate new drug development strategies, and d) differentiate clinical pain from confounding factors (e.g., drug addiction).

Perspectives

As translational pain research makes its progress, its scope is likely to be further revised and expanded. After nearly five decades of extensive basic science and clinical pain research, clinical pain management still faces enormous challenges. There are many disconnections between the overflow of information from basic science research and the effectiveness of clinical treatment of chronic pain. Currently, translational pain research is still at the stage of identifying critical issues to be addressed and exploring new research tools. However, translational pain research can be expected to play a pivotal role in advancing pain medicine. The ultimate goal of translational pain research is to maximize the yield from both preclinical and clinical studies, thereby shortening the transition period from research to clinical application.

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Table 1
New Additions of Pain Medications

Tricyclic antidepressants
Selective norepinephrine or serotonin reuptake inhibitors
Cyclooxygenase-2 inhibitors
Topical analgesics (e.g., Lidocaine patch; Non- steroid anti-inflammatory drug patch)
Alpha-2 receptor agonist (Tizanadine)
Transdermal opioid (Fentanyl patch)
Fentanyl HCL patient-controlled transdermal system
Transdermal buprenorphine
Intrathecal drugs (e.g., Ziconotide)
Triptans (5-HT receptor agonists)
Opioid receptor agonist/SNRI/SSRI combination (e.g., Tramadol)
Sublingual opioid
α_2-δ Ca^{2+} subunit blocker (Gabapentin/pregabalin)
Anticonvulsants
Others (e.g., Topiramate)

Table 2

Potential Targets for New Drug Development

Site of action	Effect	Reference
Transient receptor potential channel	Antagonist	10, 59, 91, 106
Cannabinoid receptor (CB1, CB2)	Agonist	1, 4, 8, 13, 53, 65
Potassium channels	Blocker	52, 88
Voltage-gated calcium channel	Blocker	2, 12, 83
Voltage-gated sodium channel	Blocker	42, 110, 133
Purinergic P2 receptor	Antagonist	14, 23
Nerve growth factor	Inhibitor	57, 129
Chemokine	Inhibitor	47
Proinflammatory Cytokine	Inhibitor	107, 127
Glutamate receptor	Antagonist	45, 90
Nicotinic acetylcholine receptor	Antagonist	60
Neurokinin receptor	Antagonist	67
Opioid/NMDA receptor antagonist	Combination	131
Catecholamine modulator		45
Adenosine receptor	Agonist	115

Table 3

A Partial list of Clinical Studies Using NMDA Receptor Antagonists

Clin. Model	Drug	Dose Regimen	Outcome	References
Hysterectomy	Ama	200 mg, iv, pre-op	Negative	48
Knee	Dex	200 mg, po, pre-op	Negative	124
Abdominal	Dex	120 mg, im, pre-op	Negative	58
Hysterectomy	Dex	27 mg, po, peri-op	Negative	76
CNP	Ket	> 100 mg/d, po	Positive	41
PHN	Dex	125 mg/d, po	Positive	64
PHN	Ket	0.15 mg/kg/hr × 7 d	Positive	40
NCP	Ket	400 mg/day, sc	Positive	82
NCP	Ama	200 mg/3 hr, iv	Positive	101

Legends: Knee: knee surgery; Abdominal: abdominal surgery; CNP: chronic neuropathic pain; PHN: postherpetic neuralgia; NCP: neuropathic cancer pain; Ama: amantadine; Dex: dextromethorphan; Ket: ketamine; Pre-op: pre-operative; Peri-op: peri-operative; PO: oral; iv: intravenous; sc: subcutaneous; im: intramuscular.