Assessment, quantification, and management of fracture pain: from animals to the clinic

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Abstract

Purpose of Review—Fractures are painful and disabling injuries that can occur due to trauma, especially when compounded with pathologic conditions, such as osteoporosis in older adults. It is well documented that acute pain management plays an integral role in the treatment of orthopedic patients. There is no current therapy available to completely control post-fracture pain that does not interfere with bone healing or have major adverse effects. In this review, we focus on recent advances in the understanding of pain behaviors post-fracture.

Recent Findings—We review animal models of bone fracture and the assays that have been developed to assess and quantify spontaneous and evoked pain behaviors, including the two most commonly used assays: dynamic weight bearing and von Frey testing to assess withdrawal from a cutaneous (hindpaw) stimulus. Additionally, we discuss the assessment and quantification of fracture pain in the clinical setting, including the use of numeric pain rating scales, satisfaction with pain relief, and other biopsychosocial factor measurements. We review how pain behaviors in animal models and clinical cases can change with the use of current pain management therapies. We conclude by discussing the use of pain behavioral analyses in assessing potential therapeutic treatment options for addressing acute and chronic fracture pain without compromising fracture healing.

Summary—There currently is a lack of effective treatment options for fracture pain that reliably relieve pain without potentially interfering with bone healing. Continued development and verification of reliable measurements of fracture pain in both pre-clinical and clinical settings is an essential aspect of continued research into novel analgesic treatments for fracture pain.

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Introduction

Fractures are painful and disabling injuries that can occur at any age but are particularly prevalent in 40–50% of women and 13–22% of men with osteoporosis [1,2]. The number of patients in the United States with osteoporosis or low bone density will continue to rise with the aging of the population, leading to an increased prevalence of bone fractures in future years [3]. Not only is increasing age leading to a greater prevalence of osteoporosis and associated bone fractures, it is also a risk factor for impaired fracture healing and elevated bone pain [4,5]. Fractures with impaired healing can be extremely disabling due to ongoing pain, resulting in loss of function and decreased use of the affected extremities. If pain levels reach intolerable levels, it can prevent patients from adequately loading and using the fractured bone, thus causing a loss of muscle mass and further compromising fracture healing. Indeed, it is speculated that pain is the primary determinant of noncompliance with physical therapy and rehabilitation from orthopedic injuries [6••, 7]. Inadequate pain control immediately following fracture (acute period) and up to 3 months following fracture, while the bone and soft tissues are healing (subacute period) is the greatest predictor of long term chronic pain 7 years after a fracture [8]. For this reason, adequate pain management during both the acute trauma phase and the extended recovery period of orthopedic patients is necessary to improve the quality of life of the patients and for successful bone healing.

The reasons why fracture pain persists during and following the healing process are poorly understood. While pain is nearly always anticipated during the acute period following fracture or orthopedic surgery, the extent to which patients experience pain and the duration of pain varies greatly, depending on a multitude of factors, including: age, sex, BMI, and genetics [9]. In clinicopathological terms, bone pain can be separated into two categories; subacute fracture pain and maladaptive chronic pain within the affected limb. Fracture and subacute fracture pain are important causes of restricted physical activity in older persons [10]. The development of complex regional pain syndrome (CRPS) within the affected limb is characterized by ongoing pain and signs of inflammation, including edema and vascular disturbances [11]. As illustrated in Figure 1, bone fracture pain is complex and influenced by integration of sensory, emotional, and perceptual information received by many areas of the brain [12]. Pathophysiologic stress, including depression and anxiety, poor coping strategies, and decreased self-efficacy greatly alter the perception of pain, thus these factors are important to measure and track in both pre-clinical and clinical pain studies.

Because efficacious pain management is so critical for successful bone fracture healing, it is critical to assess patient-reported pain levels within the clinical setting and fracture-induced nociceptive behaviors in animal fracture models [13]. The assays currently used to assess nociception in animal models of bone fracture have many strengths and weaknesses. Understanding the limitations of currently used behavioral assays, which endeavor to accurately and reproducibly assess post fracture pain, is crucial for interpreting studies to

identity pain mechanisms and develop new effective therapies for the management of fracture pain that are superior to the current controversial first line treatments, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

Animal Models for Fracture Pain Assessment

Animal Fracture Models Used to Create Fracture Pain

The first process in assessing nociception in an animal model is recreating a model that will elicit behavior which might be associated with pain in the rodent. There are a variety of preclinical rodent models of long bone fracture which have traditionally been used to assess fracture healing: generation of a cortical hole, osteotomy, and the 3-point, or Einhorn, model. With the cortical hole model, a surgical incision is made to expose the bone and then a drill is used to remove a small cylindrical section of bone [14]. A single hole can either be drilled through the cortical bone into the bone marrow or through both cortices to create a hole penetrating the entire thickness of the bone. Osteotomies are typically created using a saw-like device that transects the bone. A single cut can be made to mimic a fracture, or the bone can be cut in two locations to remove a small segment of bone. When a bone segment is removed, the bone must be stabilized to be the same length prior to the osteotomy using plates or a replacement material, such as an isograft or synthetic scaffold, to fill the gap of the segmental defect [15]. Osteotomies are often stabilized via an intramedullary rod or pin. Segmental bone defects, particularly critical sized bone defects that are large enough so that they will not heal without intervention, are excellent for modeling more severe traumatic bone fractures that require intensive clinical intervention. While cortical hole and osteotomies are commonly used to assess fracture healing, the first fracture model used to specifically monitor fracture pain behaviors in rodents was the 3 point, or Einhorn, model [16•, 17,18•]. The Einhorn fracture model is a 3 point break model performed by placing the bone to be fractured on a surface with two points and then the third point is centered above the bone between the two heads below. The third point is then brought down upon the bone to create the break. This model can be used to create a closed fracture in a living animal under anesthesia using the 3 point bending device or guillotine mechanism [18]. Many models first stabilize the bone with an intramedullary rod or pin before using the 3 point device to fracture the bone. All three of these fracture models could be used to study fracture pain; however, the majority of fracture pain behavior research has been conducted using the Einhorn model to create a closed femoral fracture. This is likely because the Einhorn closed fracture model simulates a simple closed fracture, which is most often seen clinically.

Animal Pain Behavior Overview

Clinical fracture pain is a perception that is influenced by psychological and experiential factors, thus an animal fracture model will not recapitulate completely all of the factors that contribute to clinical pain. Despite this limitation, considerable effort and progress has been made in objectively modeling and quantifying nociception in animals, specifically in rat and mouse models. Unlike in the clinical setting, where patients can verbalize how they perceive spontaneous and evoked pain, preclinical investigators rely upon expression of nociceptive behaviors to assess animal pain levels. Consistent animal behaviors in response to noxious stimuli are often referred to as pain behaviors, as ascending and descending pain pathways

are activated by noxious stimuli in wounded animals [19]. As mentioned previously, psychological and experiential aspects of pain perception cannot be assessed in rodents but are controlled for as much as possible. Due to inherent variability in baseline nociceptive behaviors, even in inbred mice and rats, the optimal experimental design for pain behavior assessment includes a baseline measurement of each behavioral modality, prior to any noxious intervention, including bone fracture. Pain behaviors are generally described in two categories in both humans and animals, spontaneous pain behaviors and evoked pain behaviors. There are numerous behavioral tests that have been used to assess many different types of pain, including inflammatory, neuropathic, arthritic, muscle, cancer, and incisional pain. Although evoked behaviors traditionally have been used more frequently to assess nociceptive thresholds, the assessment of spontaneous pain and risk/reward behaviors has increased over the past decades to emulate the challenges faced by patients and to enhance the translatability of preclinical pain research. For this review, pain behaviors that have been used and shown to be sensitive for the assessment of fracture pain will be highlighted. Lower limb fracture pain can be assessed directly by examining the effects of body weight loading onto the fractured limb or indirectly by assessing hypersensitivity of hindpaw skin of the affected limb to mechanical or thermal stimulation [20]. Hypersensitivity of the sensory neurons innervating the bone at the fracture site constitutes primary hyperalgesia, whereas skin hypersensitivity represents secondary hyperalgesia or referred pain [21]. Secondary hyperalgesia is caused by sensitization of spinal cord neurons or neurons of higher order in the central nervous system [22]. Recent studies have shown that, while assessment of skin hypersensitivity is commonly used as a surrogate for fracture pain, the mechanisms that underlie primary and secondary hyperalgesia elicited by fracture differ and thus studies must be designed appropriately to examine whether putative therapeutics alter direct bone pain or referred pain [20].

Spontaneous Pain Behaviors for Assessing Fracture Pain

Spontaneous pain may manifest differently depending on the type of pain stimuli, whether that be inflammatory pain, visceral pain, bone pain, etc. [23]. For fracture pain, such as that from a closed femoral fracture in a mouse, pain can be assessed by observing time spent performing spontaneous pain behaviors over a set period of time, typically anywhere from 2–20 minutes depending on the study [16]. For most effective analyses, all spontaneous mouse pain behaviors are assessed through video surveillance of the animal [24]. There are some variations to these methods of observation such as recording the number of times a specific spontaneous pain behavior is performed over a period of time instead of recording the overall time spent performing the behavior [16]. The observations discussed below are used to quantify spontaneous pain because they are thought to mimic similar spontaneous or ongoing clinical pain.

Guarding and static weight bearing recapitulate behaviors commonly seen in the clinic, where patients protect an injured limb from external mechanical stimuli and the force of body weight loaded on to the affected limb [25]. Guarding of the injured limb is defined by the animal lifting and holding their limb against their body and is typically quantified by assessing the amount of time spent guarding the fractured limb [26]. In addition to guarding, a similar assessment for evaluating fracture pain is the observation of the number of

spontaneous paw flinches of the fractured limb over a set period of time [16, 27]. Spontaneous paw flinches are quick, instinctive paw withdrawals or movements in reaction to spontaneous pain while guarding of the limb is typically held for a longer duration than a single paw flinch. The more hindpaw flinches and time spent guarding as well as fewer vertical stands (discussed later as rearing) indicates a higher level of fracture pain.

Possibly the most reliable indicator of fracture pain is the reduction of weight bearing with the fractured limb, so that the hindpaw of the fractured limb only rests on the floor instead of pressed flat on the ground and bearing weight. Weight bearing demonstrates the level of usage and mechanical loading of the fractured limb, which is of increased importance because load-bearing bones require mechanical loading to fully heal as previously stated. This implies weight bearing is not only important in measuring the level of pain in an animal, but also for assessing recovery and healing. Weight bearing can be measured as static weight bearing or dynamic weight bearing (also involved in gait analysis; see below). For assessing static weight bearing on the hind legs, the animal is typically placed in a small restrictive container with an inclined floor so that most weight must be placed on the hind legs. Floor sensors are placed to measure the weight placed on each hind foot individually and the distribution of weight between the two hindpaws can be determined. The greater the difference between the weight distributed on the fractured limb and the contralateral limb is an indicator of greater nociception experienced by the rodent. This model has been shown to be an effective assessment for osteoarthritis, bone cancer pain, and is applicable to fracture pain [28, 29]. A known limitation of the static weight bearing method is that it is primarily suited for unilateral hind limb injuries.

Dynamic weight bearing, gait, and locomotion assays can model how the fracture pain affects the ability of patients to ambulate; assessing altered weightbearing or limping and/or compensatory accommodations in gait to prevent or minimize pain within the affected limb. Dynamic weight bearing involves calculating the fraction of weight borne on each of the individual four limbs in freely moving animals. Typically, a dynamic weight bearing system involves a floor instrument on the bottom of the cage that records pressure data as well as foot surface area for each limb to calculate the percentage of body weight placed on each limb during movement. Software such as that from BioSeb can be used to attribute pressure readings to individual paws with high fidelity [30]. As with other behavioral assessments, the rodent is allowed to acclimate to the new cage for a set period of time before data acquisition begins. Similar to static weight bearing assessment, the dynamic weight bearing technique has been shown to be an effective nociceptive test for inflammation and cancer bone pain and is useful for fracture pain assessment [31]. Dynamic weight bearing has the added benefits of not requiring restraint of the animal and having the capacity to evaluate the weight bearing of all four limbs when compared to static weight bearing assessments.

In addition to weight bearing analyses, gait and locomotive activity have been used to assess levels of pain in rodents. Modification of many different gait parameters, such as interlimb coordination, paw pressure, paw print area, stance phase duration, swing phase duration, stride length, and swing speed can be observed in unilateral injury models. Some of these parameters, such as swing duration, have been shown to be more reliable and valid parameters than others for assessing nerve recovery or pain [32]. The first discovered

method for assessing gait involved covering the animal's paw with ink and allowing it to walk freely on a piece of paper. The paper can then be scanned and the footprints analyzed to determine limping behaviors or change in stride length [33]. Newer models use an automated gait analysis tool, such as CatWalk XT or DigiGait, to track the rodent's paw prints as it walks along an elevated clear platform [34]. Lastly, some investigators use μCT to examine the mechanics of limb placement during movement [35]. Although gait was expected to be an ideal analysis of fracture pain in rodents, as alterations in gait are a primary symptom of lower limb fracture pain seen in humans, very limited changes in gait have been observed in rodents and gait alterations do not always correlate with nociceptive pain, such as hypersensitivity to mechanical stimulation of the hindpaw [35, 36]. Locomotive activity and distance traveled can be evaluated in a freely moving animal using video surveillance and associated tracking software or via monitoring the distance traveled on an activity wheel. Though behaviors such as diminished locomotion and wheel running activity may appear to be reflective of nociceptive behavior, interpretation of behavioral changes in exercise must be clearly defined as changes in locomotive behavior may both cause and/or be affected by changes in metabolic function, mood, or depression [37]. Moreover, reduced locomotion associated with acute inflammation does not always correlate with other measurements of pain, such as Von-Frey measurement [38]. Due to inconsistencies in the association of gait and locomotion with nociception, more emphasis has been placed on the use of dynamic weight bearing to assess fracture pain [39, 40]. Other methodologies such as the Basso Mouse Scale (BMS; detects differences in recovery after spinal cord injury) which includes joint movement, stepping ability, coordination and trunk stability [40•]. One advantage of the BMS scale is that it mainly focuses on hindlimb movement, rather than on graded changes in body support ability.

There also are changes in non-specific animal behaviors that are thought to reflect changes in quality of life and/or normal function due to spontaneous pain, which do not necessarily have a human behavioral correlate [21]. These include rearing behavior and grooming habits [41]. Rearing by the rodent, as defined as lifting both front paws off the floor at the same time, is another measure of spontaneous activity. Rearing is considered an exploratory behavior that occurs naturally in healthy mice with good affect [42]. Typically, animals in pain have been shown to have a decreased number of spontaneous rears which is consistent with a less outwardly focused animal. [24]. Rearing behaviors may have additional implications when evaluating fracture pain because most fracture models target the mouse femur or tibia, and rearing behaviors require increased weight bearing upon the hindlimbs. Rodents with increased pain will generally have excessive grooming behaviors with increased tending to the injured limb [24]. Excessive grooming has been used and verified as a measure of spontaneous nociceptive behaviors specifically for fracture pain [6]. Like other spontaneous behaviors, the number of rears and time spent grooming or attending to the fractured limb are recorded over a set period via video surveillance.

Evoked Pain Behaviors for Assessing Fracture Pain

Unlike spontaneous pain behavior observations, evoked pain behaviors are responses to an external application of some sort of noxious or non-noxious stimuli, including: heat, cold, mechanical, and electrical stimuli. These external stimuli can either be applied to the site of

injury (palpation) or to another site (hindpaw withdrawal behaviors). To directly correlate with clinical practice, where orthopedic surgeons palpate the fracture site to establish whether the site is painful, preclinical investigators monitor spontaneous pain behaviors before and after palpation of the fracture site to assess fracture pain [6].

Mechanical and thermal hindpaw withdrawal behaviors are commonly used to assess fracture pain due to the common availability of testing devices. The Von Frey test is thought to be especially useful for assessing increased cutaneous mechanical sensitivity, but has also been used to measure mechanical allodynia associated with fracture pain in rodents [18, 21]. To perform the assessment, the animal is placed in a cage with a mesh bottom and is allowed to acclimate while roaming freely. The animal is then challenged with a mechanical stimulus and the force required to elicit a reflexive withdrawal response is measured. For the manual model, the plantar surface of the hindpaw is stimulated with Von Frey monofilaments with predefined bending forces ranging from 10 to 120 mN. The monofilament is applied to the bottom of the paw at a perpendicular angle until the filament for a set period (typically between 2-5 seconds). The animal is observed to gage for positive pain behaviors, withdrawing or licking the stimulated paw. There are variations in the endpoints measured with Von Frey stimulation, including assessing a response frequency to individual monofilaments to determine hyperalgesia (enhanced response to a noxious stimulus force) or allodynia (a novel response to a non-noxious stimulus force) or by determining the 50% paw withdrawal threshold (PWT) by beginning with the lowest bending force filament and gradually escalating the force applied to the paw until the force corresponding to a 50% withdrawal rate is determined [43]. Thus, a lower PWT corresponds to a higher pain level. This approach has been optimized over time to reduce the amount of test applications and control for the extent of investigator interaction with the animals [44, 45]. These methods are fairly time consuming, require repeated stimuli that can cause sensitization or learned premature withdrawal by the animal, and have large observer to observer variability [46••]. To decrease exposure of the animal to multiple stimulations, the Electronic Von Frey was developed. This device determines PWT by applying one non-bending Von Frey filament to the paw of the animal with increasing force until the animal withdraws its paw. Software accompanying the instrument records the force at which the animal removes its paw [47–50]. This method drastically reduces the number of applications needed for each animal in order to determine PWT and reduces the time required to perform the experiment; however, the test still requires an experienced researcher to help determine between false positives and true pain behaviors. Thermal hyperalgesia is also evident in animal models of fracture pain, measured by the hot plate test [18]. The hot plate test includes placing the rodent on a metal hot plate set at a constant temperature typically ranging from 50-55°C and observing how long it takes for the animal to express a nociceptive behavior such as paw withdrawal, licking, or jumping [51]. Alternatively, thermal hyperalgesia secondary to bone fracture could be measured using the Hargreaves test, where a radiant heat source is focused on a hindpaw and the temperature ramps until the animal withdraws the paw [52]. The Hargreaves test is advantageous because it allows for the fractured limb to be tested and compared to the contralateral limb. As mentioned previously, the reliability of skin hypersensitivity as a surrogate for assessing skeletal pain is still a topic of debate, since Guedon et al demonstrated that therapies such as anti-P2X3 were able to relieve skin

hypersensitivity measured by evoked pain behaviors but did not relieve spontaneous skeletal pain behaviors from bone cancer pain [53•].

Clinical Fracture Pain Assessment

With the creation of pain as "the 5th vital sign" by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO, now called The Joint Commission) and subsequent adoption and support from the Veterans Health Administration (VHA), there is an obligation for physicians and healthcare professionals to evaluate, treat. and alleviate a patient's experience of pain [54]. The clinical setting has historically used a basic 11-point verbal numeric rating scale (NRS) or visual analogue scale (VAS, 0 = no pain, 10 = the worst pain ever imagined) [55, 56], which is generally a reliable and valid measure of pain intensity [57]. With pediatric populations, often based on the level of neurologic maturity and arithmetic development, the Faces Pain Scale - Revised [58, 59] is used to assess fracture pain. Orthopedic surgeons rely on these pain scales to evaluate pre-surgical, post-surgical, and change in pain during the fracture healing process. However, data have shown that these scales, while optimal for acute measurements, are not sufficient for chronic pain management and fracture evaluation [60]. With current methods there often is a discrepancy between the multidimensional aspect of pain and the unidimensional methods that are used in the evaluation of pain. The English language has evolved to portray many aspects of the quality of pain, yet often standard methods of analysis evaluate only the intensity of the pain experience [61].

Biopsychosocial Factors

While quantification of pain is assessed pre-operatively and post-operatively, there have been associations between biopsychosocial factors and chronic pain post-surgery. Several studies have shown that pre-operative factors such as depression, anxiety, self-efficacy, catastrophizing, smoking, or a history of substance abuse correlate to both acute and chronic post-surgical pain[13, 62•, 63, 64•, 65, 66]. Furthermore, data indicate that these correlations are independent of any single surgical model [64]. Therefore, patients could be pre-operatively screened for biopsychosocial factors using the Pain Health Questionnaire-Depression [67, 68]. Pain Anxiety Scale [69]. Pain Self Efficacy Questionnaire [70], and Pain Catastropliizing Scale [71], each of which is assessed with Likert Scales of varying benchmarks. Additionally, pre-operative screening for health factors such as smoking or substance abuse could predict post-surgical pain. Due to the short nature of these pre-screening questionnaires, it warrants consideration that patients pre-operatively complete these questionnaires as a new "standard of care". Further analysis, potential screening, and intervention for these correlations could reduce the prevalence of post-surgical pain as it relates to fractures.

Pharmacological Treatment

Pain during fracture healing is common and management is complex. Currently, the two primary treatments used to manage pain for trauma-induced fracture and post-surgical pain are opioids and NSAIDs. Both drugs have been shown to have negative off-target side effects and neither has demonstrated the ability to alleviate pain completely. Narcotics are

the standard of care for the majority of orthopedic patients. This choice of drugs for pain is largely due to the presence of significant perioperative pain and the necessity for adequate analgesia in patient care in the postoperative setting (Figure 1). Animal models have shown that administration of morphine produces a dose-dependent reduction in spontaneous pain behaviors such as guarding and flinch as well as increased levels of weight bearing 7 days post fracture [27]. However, the use of opioids raises many concerns including the recent identification as a major contributor to the current opioid epidemic. These concerns include preclinical and clinical studies which indicate that opioids can actually elicit dose-dependent increases in pain [40, 62, 72, 73]. Additionally, opioids are known to elicit cognitive impairment as well as tolerance and addiction. Furthermore, many of the complications and side effects associated with opioids have been shown to be more prevalent in older patient populations, which is even more concerning given the increase in prevalence of osteoporosis in older patients [74]. There are additional concerns that opioids alone or with injury can actually increase long-term pain and create opioid induced hyperalgesia (OIH) [75–78]. Opioid receptors are present on osteoblasts which has led some to hypothesize that opioids may also impair fracture healing [79].

NSAIDs (cyclooxygenase [COX] inhibitors) block the COX enzymes and reduce prostaglandins throughout the body, which is effective at relieving pain for various musculoskeletal disorders [27, 80]. However, this class of drugs also produces dose-dependent negative side effects including gastrointestinal bleeding and kidney damage. Of particular concern with fracture pain is the negative impact on skeletal health and healing of fractured bones [81]. Animal studies suggest that COX inhibition diminishes tibial bone healing due to retardation of callus formation and bone repair [81, 82]. Some clinical studies suggest that NSAIDs do not affect fracture repair, whereas others demonstrate a negative effect of the drugs [83, 84]. Current recommendations conclude that NSAID use is warranted in fracture healing, as benefits outweigh the risks [85, 86]. Due to a lack of a causal relationship to fracture nonunion, the use of NSAIDs facilitates lower dose or complete avoidance of opioid prescriptions post-fracture repair. Such regimens have been shown to lower pain scores, lower adverse effects, and improve patient satisfaction scores [87•]. Despite these results, many physicians, especially those in the United States, avoid the use of NSAIDs for patients recovering from bone fractures due to the belief that NSAIDs impair bone healing [88, 89].

The United States Compared to Other Countries

An additional aspect to address is the disparity between opioid use in the United States as compared to other countries. Two studies highlight differences in opioid prescriptions and patient satisfaction that indicate underlying psychosocial and cultural influence. A comparative study between a United States and a Dutch hospital looked at the difference in opioid prescriptions and patient satisfaction of pain management for the treatment of ankle fractures [90•]. The study analyzed two different time points: post-operative day 1 and at suture removal (approximately 10-14 days). At each time point, patients completed a 5-point Likert scale to rate their pain and satisfaction with pain management.

On post-operative day 1, patients using opioids reported significantly worse average pain scores (3.0 vs. 2.5; p < 0.05). More patients in the United States also reported consuming opioids rather than alternatives such as acetaminophen or NSAIDs (100% vs. 67%; p < 0.001). Additionally, the majority of Dutch patients (15 of 20) that did use an opioid prescription opted for tramadol, a weak opioid agonist, as compared to Americans who used strong opioid agonists, such as oxycodone or hydrocodone. On post-operative day 1, there was no difference in patient satisfaction with pain management in the opioid vs. non-opioid patient populations. Following suture removal, patients using opioids reported significantly worse average pain scores (2.6 vs. 2.1; p < 0.01). More patients in the United States continued to consume opioids rather than alternative options (70% vs. 13%; p < 0.001). At suture removal, patients who were not taking opioids in either group reported greater satisfaction with pain management than those taking opioids (4.5 vs. 4.1; p < 0.05). In both the United States and Dutch populations, results from the 5-point Likert analysis indicated that the use of opioid medications was associated with greater pain and less satisfaction with pain management.

An additional study compared United States and Vietnamese patients in the treatment of closed femoral shaft fractures [91]. At 14 days post-surgical repair, Vietnamese patients received on average less morphine equivalents than United States patients (0.9 mg/kg/day vs. 30.2 mg/kg/day). Despite substantially higher doses of opioids. United States patients reported a greater dissatisfaction with pain management. Additionally, between the United States and Vietnamese groups, there was a significant difference in anticipation and expectation of fracture pain post-repair (4% vs. 76%). Despite the increase in opioid consumption. United States patients, on average, reported greater pain levels post-fracture. Furthermore, other countries report that equal or greater satisfaction in pain management can be obtained without the use of opioid medications. These findings could be a result of one of two factors. First, increased opioid intake by Americans could increase pain scores by OIH. Alternatively, these data may indicate a role for cultural and social influences on pain perception and management [92].

Conclusions: Evolving Landscape of Pain Management in the Era of the Opioid Crisis.

Current treatment options for the management of fracture pain are insufficient. Given the importance of managing fracture pain to maximize both patient comfort and fracture healing, the development of new analgesics that do not compromise fracture healing is a prominent need currently facing the medical community. The rising incidence of fractures in the aging United States population exacerbates this issue. In order to safely develop and test potential analgesic therapies, there must be an adequate preclinical model of implementing and assessing fracture pain. Because pain is a subjective feeling, assessment of nociception in non-communicating subjects such as animals is done through observations of "pain behaviors". While no single behavioral observation is completely sufficient to truly evaluate fracture pain, using a combination of various pain behavior observations such as spontaneous pain behaviors and evoked pain behaviors has shown to have strong correlations with nociception in non-communicating subjects (see Table 1 for a summary). The accuracy

of evoked cutaneous pain behaviors with regard to assessing skeletal pain remains a topic of debate, but spontaneous pain behaviors such as dynamic weight bearing analysis and guarding or flinching behaviors continue to provide dependable insights into fracture pain in preclinical models.

There is variation in each individual's response to nociceptive stimuli and likewise, varying responses to analgesic treatments, thus dependable pain assessment tools also are needed in the clinic to monitor the effectiveness of current and future therapies for each individual patient. Keeping in mind that pain is a multifactorial experience that involves both nociceptive stimuli and biopsychosocial factors, these additional components must be considered when constructing assessment tools for pain. Data suggest that pre-screening and/or post-screening for certain biopsychosocial factors could indicate consideration for alternate pain management regimens in at-risk populations for chronic post-surgical or fracture pain and become the new "standard of care".

Due to controversy with bone healing and nonunion, current management of acute and chronic fracture pain in the United States is achieved through opioids, rather than NSAIDs. Despite data suggesting opioids produced dose-dependent increases in post-surgical pain and OIH, they remain the current standard of care. In light of international comparative studies indicating opioids produced greater pain intensity and decreased satisfaction with pain management, the future of fracture pain management could shift to alternate regimens such as low dose opioids, inclusion of NSAIDs, regional nerve blocks, and various other molecular mechanism-based targets. With continued advancement in the assessment and quantification of fracture pain in both preclinical and clinical settings, we gain the tools needed to discover new therapies and improve current management of fracture pain.

Acknowledgements

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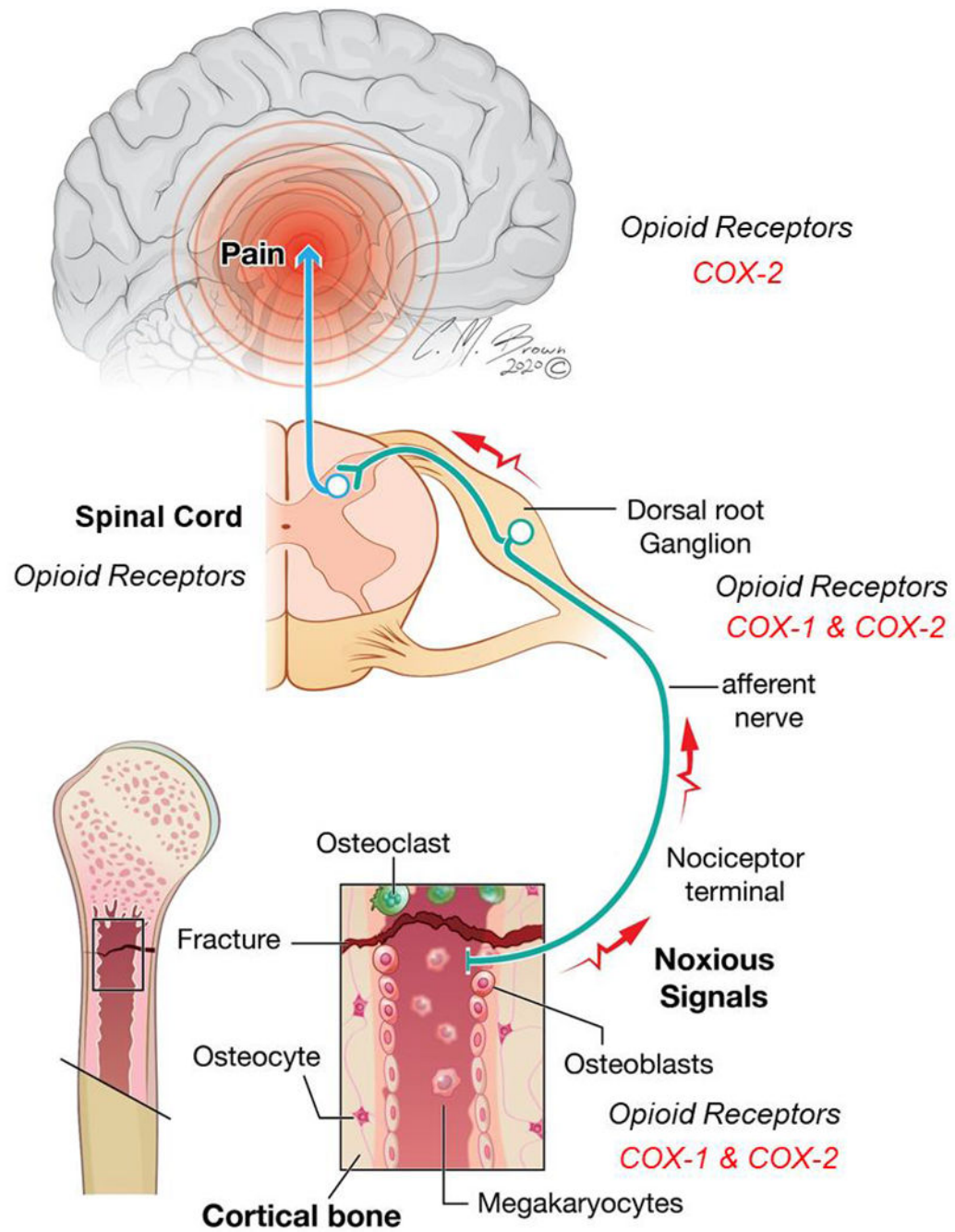
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Figure 1.

Anatomic levels of nociceptive processing following bone fracture. Upon injury, inflammatory mediators, including prostaglandins, are released locally by a variety of non-neural cells and the nervous system. Biosynthesis of prostaglandins are attributed to two different enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and are blocked by nonsteroidal anti-inflammatory drugs (NSAIDs). Opioid receptors are critical in the modulation of pain following fracture. Opioid receptors are expressed throughout the

nociceptive neural circuitry in the peripheral nervous system, spinal cord, and critical regions of the brain involved in reward and emotion-related brain structures

Table 1.

Assessment of Fracture Pain Behaviors

Spontaneous Pain Behaviors		
Method of Pain Assessment in Animals	**Key Elements Assessed**	**Clinical Correlate**
Guarding/Spontaneous Flinches	Time spent lifting and holding affect limb against body/number of spontaneous paw flinches over set period of time	Patient protecting injured limb from external mechanical stimuli
Static Weight Bearing	Relative difference of weight place on affected limb versus healthy limb when stationary	Relative force of body weight patient loads onto affected limb while standing
Dynamic Weight Bearing/ Gait Analysis	Fraction of weight borne on each limb while freely moving/ Interlimb coordination, stance phase duration, swing phase duration, stride length, and swing speed	Presence of limp or other abnormal gait mechanics in patient
Locomotive Activity	Distance traveled by freely moving animal over set period time	Patient activity level
Rearing/Grooming Behaviors	Time spent lifting both front paws off the floor at the same time (exploratory behavior)/Time spent groom fur and tending to injured limb (note: more grooming correlates with more pain)	Patient ability/drive to perform daily activities (note: increased daily activities inversely correlates with pain)
Evoked Pain Behaviors		
Method of Pain Assessment in Animals	**Key Elements Assessed**	**Clinical Correlate**
Mechanical Von Frey	Amount of mechanical force required to trigger reflexive withdrawal response	Physician physical palpation of injured limb and assessment of pain response
Hargreaves Test (Thermal hyperalgesia)	Temperature required to trigger reflexive withdrawal response	Not commonly performed in clinical setting