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An overview of animal models of pain: disease models and outcome measures

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Abstract

Pain is ultimately a perceptual phenomenon. It is built from information gathered by specialized pain receptors in tissue, modified by spinal and supraspinal mechanisms, and integrated into a discrete sensory experience with an emotional valence in the brain. Because of this, studying intact animals allows the multidimensional nature of pain to be examined. A number of animal models have been developed, reflecting observations that pain phenotypes are mediated by distinct mechanisms. Animal models of pain are designed to mimic distinct clinical diseases to better evaluate underlying mechanisms and potential treatments. Outcome measures are designed to measure multiple parts of the pain experience including reflexive hyperalgesia measures, sensory and affective dimensions of pain and impact of pain on function and quality of life. In this review we discuss the common methods used for inducing each of the pain phenotypes related to clinical pain syndromes, as well as the main behavioral tests for assessing pain in each model.

1. Introduction

Pain, both acute and chronic, remains a significant health problem despite tremendous progress in understanding of its basic mechanisms. The Institute of Medicine reports that more than 100 million Americans experience chronic pain – more than heart disease, cancer and diabetes combined. Further, pain costs the United States half a trillion annually, measured in terms of health care usage, lost wages, and impact on quality of life. Despite the prevalence and impact of pain, it is extremely difficult to treat, and few basic science advances have been effectively translated to the clinical setting over the last several decades.

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Perspective: Understanding animal models and outcome measures in animals will assist in translating data from basic science to the clinic.

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Animal models of nociception (pain) date back to the late 19th century and have been crucial in our understanding of pain processes[201]. Since then, there have been a large number of animal models of disease developed to better understand pain from a variety of disease states, both acute and chronic, and have proven useful in further advancing disease-specific questions and processes [14;16;74;164;207]. It has become increasingly clear that that pain is a heterogenous phenomenon that differs widely based on the affected tissue (skin, muscle, joint, viscera, etc.) [78;136;171] and the mechanism of injury (thermal, mechanical, inflammatory, neuropathic, etc) [50;124;165].

Animal models of nociception have two important components: the method of insult and the subsequent end-point measurement. The most appropriate models, whether an injury, application of chemical agents, or other manipulations, should produce nociception by recapitulating the mechanisms of specific clinical conditions. Similarly, measures of nociceptive behavior must not only detect pain-like responses, but should do so in a manner consistent with the clinical experience of pain. Measures of reflexive behaviors such as withdrawal thresholds to noxious stimuli have been used for decades to examine mechanisms of pain. These have clearly proven useful in advancing our understanding of the physiological basis of nociception, identification of neurotransmitters, receptors, intracellular messengers, and genes involved in pain behaviors; and better understanding of existing pharmacological and non-pharmacological pain treatments [10;37;5056;207;208]. Further, over the last several decades, the pharmacological action (e.g. efficacy, potency, duration of action) of a broad spectrum of analgesics to reduce reflexive sensory responses in rodent models of acute nociception and chronic pain have demonstrated consistent correspondence to human analgesia [210].

It is clear that other behavioral tests can also produce valuable information that may not be gained solely from reflexive tests. As pain is a multidimensional experience [122] that includes a sensory experience of pain which can be dissociated from unpleasantness, it is useful to have measures that assess spontaneous pain behaviors, cortical processing and decision making, and physical activity levels (reviewed below). Further, since pain has significant impact on function and quality of life (see IOM Report on Pain), measures that reflect these more complicated consequences of pain in animals will also help improve our understanding of mechanisms and diseases.

There has recently been significant debate over the most appropriate animal models of pain and which behavioral measures should be used. This debate focuses on the failure of the translation of basic science data into effective analgesics and has led to a re-examination of the utility of animal models of pain and behavioral measures for screening new potential analgesics. One well-known failure is that of the neurokinin-1 receptor antagonists (substance P) [77]. Several reasons have been suggested for these failures [125]. One concern is the reliance of studies on reflexive measures, and it has been suggested that additional measures of supraspinal integration that use non-reflexive pain behaviors should be included, such as operant learning measures, spontaneous nocifensive behaviors, and quality of life or physical activity measures. Another concern is the use of animal models of disease that do not reflect the clinical condition the experimenter is trying to model, such as using inflammatory pain in animals to study chronic low back pain. Despite the failures, successes based on animal models have been noted, including the use of TNF-alpha antibody therapy for rheumatoid arthritis and targeting N-type calcium channels (ziconotide) and potentially nerve growth factor antibodies (tanezumab) for chronic pain [2;7;94;166]. Other therapies may provide mixed results, as seen in targeting TRPV1 with systemic antagonists. This has proven difficult because of significant side effects (i.e. hyperthermia), but desensitization of TRPV1 channels with capsaicin creams does significantly reduce pain in several different pain conditions (for review see [88]).

The argument presented here is that animal models should be based on 1) understanding the clinical disease presentation and pathology (i.e. face validity) and 2) behavioral measures should be used that assess issues particular to that disease. For example, osteoarthritic knee pain generally has mild pain while resting (spontaneous pain) but significant pain with movement (evoked pain). On the other hand, people with neuropathic pain generally have significant spontaneous pain as well as pain with touch or pressure (evoked pain). Therefore, multiple outcome measures should be examined in animal studies, and these outcomes should reflect behavior observed in the pain condition in humans for which the experimenter is studying.

It should be pointed out as well that failure of an analgesic to relieve symptoms in a clinical trial is not necessarily directly attributable to a basic failure of the research effort in animals. As with animal models, clinical trial design should also consider basic research findings, and multiple outcomes measures should be considered that include not only resting pain, but movement pain, hyperalgesia, function and quality of life measures. Each of these constructs is unique and may reflect a different outcome. As an example, using a non-pharmacological treatment (TENS), Sluka and colleagues have repeatedly shown a measured reduction of hyperalgesia (increased sensitivity to evoked pain measures) in animal models of disease [174]. On the other hand, a great majority of clinical trials have measured spontaneous pain in human diseases [174]. Although TENS had no effect on spontaneous pain in postoperative pain, osteoarthritis, or fibromyalgia, it significantly reduced walking pain and hyperalgesia in these populations [44;154;198]. Most clinical trials rely on measures of subjective pain ratings, yet since however pain impacts nearly all aspects of a person's life, including function, activity, and quality of life it is not always clear which of these a change (or lack thereof) in pain ratings was the main driving factor. We propose that clinical trials should incorporate not only pain measures at rest, but also evoked pain measures and function and quality of life measures. Indeed, experts in clinical pain research, under the name IMMPACT (*Initiative on Methods, Measurement and Pain Assessment in Clinical Trials*), proposed guidelines for the measurement of pain treatment outcomes across multiple domains: pain, physical function, emotional function, global improvement, symptoms and adverse events [57;194]

Thus, the present review is designed to give a better understanding and brief review of the available animal models of disease which include inflammatory, neuropathic, muscle, joint, visceral, cancer, and postoperative pain. We will provide a general overview of available models and assessment of their usefulness. We will also review measures of pain behaviors in animals and will include evoked/reflexive, spontaneous, and affective pain behaviors as well as measures related to function and quality of life. Having a better understanding of both the disease models and the behavioral measures will assist investigators in developing an appropriate set of experiments to better test mechanisms and potential treatments.

2. Outcome Measures of Pain Behavior

The methodology to quantify pain behavior is relatively common across the various animal models of pain. One way that the methods can be categorized is based on whether the primary outcome measure is reflexive or non-reflexive. Common applications of reflexive and non-reflexive measures to specific models are summarized in Table 1. In some instances, quantification of the organism's natural or ongoing activity can be used to examine pain.

2.1. Reflexive Pain Tests

Reflexive pain tests evaluate evoked behavioral responses after the application of heat, cold, mechanical, and electrical stimuli. These reflexive pain tests activate nociceptors at the site

of testing and trigger localized, stereotyped motor responses. Many of these responses can occur in the absence of supraspinal activation; however, they are modified by supraspinal sites. These responses require an intact motor system. Reflexive behavioral tests of evoked responses most closely mimic human studies of enhanced response to noxious stimuli (hyperalgesia), which is distinct from pain in response to innocuous stimuli (allodynia) and pain at rest (spontaneous pain). Hyperalgesia in people with fibromyalgia (pressure pain thresholds) is significantly correlated with movement-evoked pain and pain on the brief pain inventory (average of current pain, worst pain over 24h and best pain over 24h [39]; all of which take into account evoked pain. Thus, reflexive tests may give insight into evoked pain responses in human subjects.

Reflexive tests can be applied at the site of injury or outside the site of injury. Changes in threshold or response to noxious stimuli at the site of injury is termed primary hyperalgesia and is well accounted for by changes in signaling (sensitization) of nociceptive primary afferents. Changes in threshold or sensitivity outside the site of injury or enhanced sensitivity that persists without peripheral injury, termed secondary hyperalgesia and is well accounted for by sensitization of neurons in the spinal cord or higher in the central nervous system. Patients with chronic pain often have symptoms consistent with both primary and secondary zones of hyperalgesia, and the secondary zone often tends to spread with time to more regions outside the original site of injury [68]. Since the underlying mechanisms associated with primary and secondary hyperalgesia are different [65], understanding the site of testing is important for interpretation of data and comparison across published literature.

2.1.2. Thermal—One of the earliest developed methods of thermal testing is the **Tail Flick Test**, where a heat stimulus is applied and the latency to remove the tail is recorded [43]. The tail flick test is a spinal reflex occurring in spinalized animals [51]; however the tail flick latency is modified by brainstem and cortical sites [1;12;71;84;85;109;161]. Subsequently, the **Hot-Plate Test** was developed and involves recording the latency for either withdrawing the paw from the hot-plate or licking the paw [209]. The act of choosing which paw to lift to avoid the hotplate is believed to require supraspinal structures indicating that the hot plate test goes beyond nocifensive reflexes and requires integration in higher structures. Finally, the **Hargreaves test** was developed to deliver a more localized test of heat sensitivity and involves the application of heat to the hindpaw of rodents [74]. The Hargreaves test presents a benefit over hot plate testing in some models of pain because a control and experimental paw can be tested within the same animal.

2.1.3. Mechanical—Behavioral measures of mechanical sensitivity are commonly used to measure allodynia (a painful response to a non-painful stimulus) and hyperalgesia. Originally used to test mechanical sensitivity in humans [201], mechanical withdrawal thresholds of the paw using von Frey filaments is commonly used in rodents [54]. An alternative approach to measuring thresholds is to examine the response frequency to repeated application of a single von Frey filament [170;176]. Von Frey filament testing measure cutaneous hyperalgesia or allodynia and is thus most useful for mimicking clinical conditions with enhanced cutaneous sensitivity such as neuropathic pain, postoperative pain, inflammation, or even osteoarthritis [11;60;110;155;195;198].

A number of additional pressure application management systems have been developed to measure mechanical evoked pain responses. Use of mechanical pressure applied to a muscle, joint, or paw is done with a dolorimeter, calibrated forceps, or the Randall-Selitto analgesiometer [9;156;163;169]. In all of these tests, the latency to withdrawal or vocalization is used as the end-point, and the animal is restrained. When applied over a muscle or joint, calibrated forceps have been validated to stimulate deep, but not cutaneous,

tissue [169]. Measuring withdrawal responses to pressure applied to deep tissue using a dolorimeter, tweezers, or Randall-Selitto device produces results similar to decreases in pressure pain thresholds commonly observed in clinical pain conditions such as fibromyalgia, myofascial pain or osteoarthritis [5;15;63;83].

In general, the measure of reflexive pain behavior has been useful for studying underlying mechanisms associated with allodynia and hyperalgesia. The ability to apply specified thermal intensities, mechanical forces, and concentrations of chemical stimuli allows for the generation of precise stimulus/response functions. Based on the "control" function, any leftward or rightward shift in such a function can be used to examine increases or decreases in response to normally innocuous stimulation (allodynia) or response to normally noxious stimulation (hyperalgesia). In addition, the ability to quantify the nature of the evoked response has been useful in correlating electrophysiological and biochemical signaling with measured pain behavior. It has been recognized, however, that measures of pain based on reflexive responses might not fully capture the pain experience. In recent years, a number of unique non-reflexive approaches have been developed to measure pain in different animal models of disease.

2.2. Non-Reflexive Pain Tests

2.2.1. Spontaneous Pain Behavior—One of the most common measures of spontaneous pain behavior is the quantification of paw elevation and paw licking following injection of an inflammatory compound such as dilute formaldehyde (formalin) [55]. The quantification of such spontaneous behaviors has been performed following application of other substances such as capsaicin and mustard oil [40]. Similarly, quantification of writhing behaviors after an intraperitoneal injection of a painful drug can be useful to quantify visceral pain models [20]. Concentration and volume of chemical stimuli can be manipulated, and attention to the condition is recorded. The development of the formalin test was valuable since it was one of the first procedures that produced a "tonic" response. It is unclear, however, what clinical conditions formalin, mustard oil, or acetic acid mimic.

A semi-quantitative measure of paw guarding has been used in models of joint pain, neuropathic pain, and postoperative pain to examine spontaneous behaviors [24;179]. More quantitatively, limb guarding has been determined by examining weight bearing on the limbs during a short period of walking (CatWALK) [67]. Limb guarding is a common clinical manifestation in people with joint, neuropathic and postoperative pain.

Paradigms allowing for self-administration of analgesics have been used, allowing rodents to indicate the pain reducing and reinforcing effects of some drugs [118]. Such protocols typically involve drug self-administration of opioids in inflammatory and nerve injury models [38;114;119] and recently with (R,S)-AM 1241, a CB_2 agonist, in a neuropathic pain model [70].

Preference for analgesics can also be investigated using the Conditioned Place Preference (CPP) and has been tested in models of neuropathic and inflammatory pain [167;182]. During a preconditioning phase, subjects are placed in a CPP box with 3 compartments consisting of a neutral middle chamber and chambers on either side that are distinct with differing visual, textural, and olfactory cues. Then drug conditioning trials are run with the analgesic drug given in one of the two chambers, which provides the opportunity for the development of an association with the analgesic to a certain chamber. During testing, amount of time spent in the drug-paired chamber indicates a preference. Place preference induced by pairing pain relief with a distinct context is argued to reflect ongoing or spontaneous non-evoked and non-reflexive pain.

2.2.2. Avoidance of Evoked Stimuli—Measures that allow animals to avoid painful stimuli are useful because they can be used to test the unpleasant component of pain. This is important because although conditions may have similar sensory thresholds, the aversiveness of the pain may differ.

The Thermal Escape Test provides an opportunity for rodents to indicate preference for escaping thermal stimuli [120]. The apparatus is constructed of a two-chamber box where the temperature of each chamber floor can be manipulated, and place preference or latency to withdraw from the platform is recorded. This is different from hot plate testing, in which animals are presented with a single floor temperature which they cannot escape.

Conditioned Place Avoidance (CPA) is similar to the CPP paradigm in that animals are pre-conditioned, but during conditioning, animals are injected with a noxious substance (such as formalin). On the subsequent test day, chamber preference is measured in the absence of a pain-producing injection [89]. Quantifying chamber preference is treated as an indication of the aversiveness of a condition. Clinically, people with pain, particularly chronic pain, avoid stimuli that cause pain. An issue with the CPP and CPA paradigms is that they involve a significant learning component, and there is a risk of confounding factors in the event that analgesic treatment (or pain itself) impair cognitive functioning.

The **Place Escape Avoidance Paradigm** (PEAP) has been useful in assessing the aversive quality of noxious input in rat models of inflammatory and neuropathic pain [103]. After placement in a two-chamber box, rodents are stimulated repeatedly with a noxious stimulus (such as Von Frey); the painful paw is stimulated when in one chamber and the non-painful paw in the opposite chamber. Animals indicate the unpleasantness of the stimulus by shifting to the chamber where the non-painful paw is stimulated. Modified versions of the PEAP use a chamber floor with a thermal gradient to allow animals to select the preferred temperature [127]. These tests involve activation of the anterior cingulate cortex [105], a brain site that is thought to mediate the unpleasantness of pain as shown in human imaging studies [153]. Thus the PEAP may reflect the emotional and unpleasant nature of pain in the human condition.

Orofacial pain has been measured using an operant task which trains rodents to place their face on a thermode while drinking a liquid reward [139]. After an orofacial pain condition, animals show reduced contact with the thermode and increased licking behaviors. Recently, the task has been modified to include mechanical stimuli [141] and adapted for use in mice [138].

2.2.3. Quality of Life and Function—Activity and stereotypical behaviors can be assessed for an overall indication of the effects of pain on function. Overall assessments of activity, inactivity, grooming, eating and drinking, posture, gait, and social interaction can indicate whether the animal is in pain [40]. These sessions can observe the animals in either their home environment or in a novel setting. Measurements of locomotor activity and rearing behavior has been used in inflammatory, neuropathic, and arthritic models [36;104;149;178;197] and is likely useful in other animal models of pain. Wheel running activity, a measure of physical activity in animals, is reduced in animals with acute inflammation [36;177]. Interestingly, doses of known analgesics that were effective at restoring wheel running behavior were ineffective in reducing mechanical hyperalgesia tested with von-Frey filaments, suggesting that wheel running may be an objective measure of function in pain conditions [36]. On the other hand, Basbaum and colleagues measured home cage activity over a 15 day period in inflammatory and neuropathic pain models and showed minimal difference from controls, concluding that the current animal models do not affect quality of life [197]. Future studies will be needed to confirm and refine these

techniques among different pain models. People with both acute and chronic pain show significant reductions in physical activity levels and participation in daily activities, and thus these measures have direct clinical relevance [59;172;192].

2.3. Summary

The method chosen to quantify pain depends on the pain model and the primary question that is being asked. For instance, understanding of peripheral mechanisms in neuropathic pain models may be effectively addressed using a number of reflexive behavioral testing methods. On the other hand, understanding cortical mechanisms and the modulation of pain processing in other disease states may be more effectively addressed using non-reflexive methods. Using measures of function like wheel running or locomotor activity might be a useful measure to examine reduced physical activity, a common feature in clinical pain conditions. This review is not meant to indicate that one test is better than the other, but that the researcher must consider the ultimate goal of the research when choosing to use reflexive and non-reflexive tests and, ultimately, more than one test will likely be needed to more fully translate data between basic animal studies and clinical conditions.

3. Animal Models of Disease

Multiple animal models of disease have been developed. Many of these models directly mimic a clinical condition, while others have been useful in screening analgesics and in understanding analgesic profiles. When developing a potential therapeutic or testing a long-standing therapeutic, understanding the underlying processes and disease state you want to examine is extremely important toward effective translation from clinic to basic science, and from basic science to clinic.

3.1. Inflammatory Pain Models

Animal models of inflammatory pain have used use a number of different irritants that have been injected into skin, paw, muscle, joint and visceral organs. These irritants include those that produce acute inflammatory pain associated with neutrophil recruitment as well as more sustained pain responses associated with a macrophage infiltration. Thus, they are used to model conditions with both acute and chronic inflammation, and all have been validated by showing effectiveness of opioids and NSAIDs.

Injection of capsaicin into the skin, muscle or joint activates TRPV1-containing nociceptors, produces a local neurogenic inflammation, and induces pain [187;191]. Capsaicin injection results in reflexive behavioral changes that include thermal and mechanical hyperalgesia surrounding the site of injury (the site itself becomes analgesic)and mechanical hyperalgesia outside the site of injury [168;171]. These changes correspond to primary and secondary zones of hyperalgesia mediated by nociceptor and central neuron sensitization, respectively [142;206]. Capsaicin administration can also be used as an experimental pain model in human subjects [142], allowing for translation between animals and humans.

Carrageenan, a commonly used inflammatory irritant, has been injected into paw, muscle and joint and results in an initial acute inflammation that converts to a chronic inflammation by 2 weeks [74;152]. Carrageenan injection is associated with increased sensitivity to thermal and mechanical stimuli at the site of injury (primary hyperalgesia), as well as outside the site of injury (secondary hyperalgesia). In addition there is enhanced guarding of the hindlimb, reduced weight bearing on the hindlimb, avoidance behaviors (PEAP), spontaneous pain behaviors (CPP), and reduced running wheel activity [67;74;104;149;151;152;177]. This model has proven useful in understanding acute inflammatory pain and likely mimics conditions associated with tissue injury such as sprains, strains, and myositis.

Complete Freund's adjuvant (CFA) has been injected into tail, paw, muscle and joint and results in a more chronic inflammation than carrageenan. Behaviorally, thermal and mechanical hyperalgesia occur at both the site of injury and outside the site of injury, and there is reduced weight bearing, enhanced spontaneous pain behaviors non-reflexive pain behaviors (PEAP, CPP/CPA, drug self-administration) and decreased wheel running (physical activity [30;36;113;114;146;158;167;182]. CFA is used to model chronic inflammatory pain conditions that might occur with rheumatoid arthritis or tendonitis.

3.2. Neuropathic Pain Models

Neuropathic pain is evoked by damage or disease in either the peripheral or central somatosensory system [193] and often occurs following trauma to the nervous system. Neuropathic pain can also occur following ischemia, metabolic derangement, or exposure to various toxins [41]. Several successful models have been developed to mimic neuropathic pain evoked by each of these etiologies.

Cortical or thalamic pain is induced by microinjection of excitotoxic agents such as picrotoxin or kainate into the somatosensory cortex or nuclei of the thalamus [102;144;145], and microinjection of collagenase type IV directly to the thalamus was developed to mimic hemorrhagic stroke [205]. Cortical and thalamic pain models are associated with mechanical and thermal hyperalgesia and with spontaneous pain behaviors like lifting, shaking, and decreased weight bearing of affected limbs [102;144;145;205].

Several models mimic spinal cord-injury pain. The spinal cord may be damaged directly through contusion, surgical lesions of the cord, irradiation with a laser to produce ischemic injury, or neurotransmitter-induced excitotoxicity [33;73;108;199;212;213]. These spinal cord models result in mechanical and thermal (heat and cold) hyperalgesia, as well as changes in spontaneous behaviors such as place preference [46;130].

Peripheral nerves have also been targeted in many well characterized models of neuropathic pain. Direct nerve injury models include 1) ligating or transecting the spinal nerves (SNL, or SNT), 2) ligating or lesioning the sciatic nerve (chronic constriction injury, CCI; partial nerve transection), and 3) ligating distal branches (peroneal, tibial) of the sciatic nerve (spared nerve injury SNI) [14;48;97;159]. As an alternative to direct nerve injury, injection of an inflammatory irritant (zymosan) around the sciatic nerve has been used (sciatic inflammatory neuritis (SIN))[31]. The principles of these methods may be applied to nerves other than the sciatic, such as orofacial nerves [202]. The behavioral phenotypes are essentially indistinguishable between these different peripheral nerve models, with decreased withdrawal thresholds to mechanical and thermal stimuli and spontaneous guarding behavior of affected limbs [132;189]. Furthermore, there are changes in non-reflexive (spontaneous) pain in animals with nerve injury: vocalization [101], change in spontaneous motor activity [69], conditioned place preference (CPP) [75;98], escape avoidance (PEAP)[106] social behavior such as dominance [126]. Human subjects with neuropathic pain similarly show phenotypes of spontaneous pain, dysesthesia, and thermal and mechanical allodynia [8;96;107]. A problem associated with measuring spontaneous behaviors such as these in neuropathic pain versus other types of pain is that neuropathic models can elicit sensations other than pain – numbness and tingling - that could evoke false positive responses. Both painful and non-painful somatosensory abnormalities in patients may be evaluated through the use of quantitative sensory testing (QST) in order to determine both the degree and type of sensory disturbance [211], but there is currently no means to emulate this in animals because of the need for verbal feedback.

Systemic neuropathies that are associated with conditions such as diabetes or alcoholism have also been examined. Diabetic neuropathy is induced through genetic modification of

mice or injection of streptozotocin (for full review, see [183]) and chronic alcohol use is induced by long-term application of ethanol to animals through their water or daily gavage [91;93]. There have been concerns that streptozotocin itself may have neurotoxic properties that induce neuropathy directly, rather than through an induced diabetic state. However, there is evidence that neuropathy is not induced by streptozotocin except in conjunction with hyperglycemia [45]. These models show mixed results with animals showing thermal or mechanical hyperalgesia with increased sensitivity to formalin, thermal, or mechanical hypoalgesia alone, or no change at all. The behaviors observed likely depend on multiple factors, including the model used, time of diabetes, and strain of animal [183].

3.3. Cancer Pain Models

Cancer-related pain may occur in patients as a result of the cancer itself or as a result of treatments used against cancer. Animal models have been developed for both of these etiologies. Tumor-related pain has been modeled following local xenograft of cancer cells [162] into the orofacial region to model orofacial pain [76;129] or bone to model metastasis-induced bone pain [81;82;112;117;165;203]. These models produce enhanced mechanical and thermal sensitivity, enhanced palpation-induced pain, and reduced grip force (movement-evoked pain), symptoms that are common in people with cancer pain.

In addition to pain from the cancer itself, the chemotherapies used to treat the cancer often produce peripheral neuropathy (CIPN)[21;23]. CIPN is modeled by injecting the chemotherapy agent systemically to result in increased sensitivity in animals to many of the same sensory modalities that are affected in patients with CIPN, including mechanical and thermal hyperalgesia [27;28;148]. Importantly, the CIPN models allow for research into preventative treatments against the development of the neuropathic phenotype which limits the use of these effective chemotherapy agents. However, doses adapted for animal use with the goal of inducing a CIPN-like phenotype are often lower (relative to body size and anti-tumor dose) than those used patients, and so some aspects of the CIPN phenotype seen in animal models do not fully match with patient profiles [22;123].

3.4. Arthritic (Joint) Pain Models

A number of models have been developed to mimic arthritic pain conditions. These include those associated with inflammation as well as those associated with tissue damage. Injection of inflammatory irritants such as carrageenan with or without kaolin, capsaicin, or CFA into a single joint, or CFA systemically, are most commonly used and generally mimic acute and chronic inflammation, respectively, and result in a localized single-joint inflammation. These are described above in more detail under inflammatory pain.

Injection of collagen type II antibodies (CAIA) or serum from K/BxN transgenic mice are used to model rheumatoid arthritis [34;178;200] since they mimic the pathology: widespread inflammation with the greatest effect distally, synovitis, cartilage degradation, and elevated inflammatory cytokines in the joint fluid. These rheumatoid arthritis models are associated with enhanced mechanical sensitivity of the paws and joints as well as reduced physical activity levels [178;184].

Osteoarthritis is modeled by destruction of tissue surrounding the joint. Severing the anterior cruciate ligament or performing a meniscectomy of the knee joint, or performing a partial diskectomy of the temporomandibular joint have been used to mimic osteoarthritis [111;200]. These are both associated with enhanced joint destruction, particularly of the cartilage, similar to that observed clinically in osteoarthritis [111;200]. Alternatively a single injection of monosodium acetate (MIA) results in enhanced joint destruction, inflammation, elevated cytokine levels, and pain behaviors and is used to mimic osteoarthritis [111;200].

Several pain behaviors are measured in these models, including vocalization to joint movement and decreased weight bearing on the affected limb[62;86;87;143].

3.5. Muscle Pain Models

Muscle pain has been studied in animal models using a number of approaches, generally through injection of an irritant into a muscle. The hindlimb is a common site of injection, though neck and orofacial muscles are also used. Inflammatory models of muscle pain involve injecting an irritating compound (mustard oil, carrageenan, complete freund's adjuvant, formalin, etc.) into the muscle, which triggers a robust inflammatory response [4;30;52;66;72;152] designed to mimic myositis and muscle strains in humans [115]. These compounds result in decreased mechanical withdrawal thresholds of muscle and paw, enhanced avoidance to noxious stimuli (PEAP), and decreased voluntary activity [16;79;80;149;152;175;196].

Several models have been developed to mimic more widespread hyperalgesia that is not associated with inflammation such as fibromyalgia, non-specific back and neck pain, or myofascial pain. In general these models use repeated low-intensity insults and produce long-lasting and widespread hyperalgesia. For example, repeated pH 4.0 saline injections into the gastrocnemius muscle produces a long-lasting, widespread decrease in muscle and paw mechanical withdrawal thresholds, decreases in activity levels, and central sensitization that is independent of continued nociceptive input [149;173;175;176;190]. The acid-induced animal model has been validated by showing analgesia to opioids, NMDA channel blockers, pregabalin, and exercise, but not to non-steroidal anti-inflammatories [13;140;175;214], and by showing intramuscular acid in human subjects produces local referred pain and hyperalgesia [64]. Similarly, prior exposure of a muscle to carrageenan results in a more prolonged response (decreased muscle withdrawal threshold) to intramuscular prostaglandin E2 [53]. Additional non-inflammatory animal models include injections of hypertonic saline, ATP, serotonin, and NGF and have been validated as pain-producing substances in human subjects [6;26;128;160;163;185;186]. Lastly, as stress a common trigger for muscle pain, several studies show that exposure to stressful conditions - sporadic shock, cold water, or sound induces long-lasting muscle pain [32;95;131].

Models of exercise-induced muscle pain also produce muscle hyperalgesia. The use of eccentric contractions, in which the muscle is forced to contract while lengthening under a load, produces significant tissue damage and has been used as a model of delayed onset muscle soreness [3;150;188]. On the other hand, a two hour running wheel task paired with a low-intensity muscle insult produces long lasting, bilateral muscle and paw hyperalgesia, without detectable muscle damage [177;215]. These models are used to mimic the pain produced by exercise and physical activity in human subjects with chronic pain [99;180].

3.6. Postoperative pain

Models of postoperative pain induced by a longitudinal incision made through skin, fascia, and muscle of the plantar aspect of the hindpaw or calf [24;147] were developed to reproduce the same pathology observed in surgical procedures that induce both superficial and deep-tissue injury. These result in the development of heat hyperalgesia, mechanical hyperalgesia, and spontaneous pain behaviors [147;216].

3.7. Visceral Pain

Visceral pain is typically studied by irritating the peritoneum or hollow organs of the pelvis andabdomen and observing pain behavior. Electrical current, mechanical trauma, ischemia, and chemicalshave been used as noxious stimuli in visceral pain studies [136]. Two common approaches to studyingvisceral pain are the acetic acid writhing and colorectal

distention models. The acetic acid writhingmodel is used to study the nociceptors lining the peritoneum and measures spontaneous pain. Aceticacid (0.6% v/v) is given by i.p. injection and the number of writhing events (stretching, retracting, orpressing the belly against the floor) is counted [100]. Distension of hollow organs is painful in human subjects and has been modeled in animals [136;137] . The most commonly used is distension of the colon, where a balloon inserted into the colon is inflated, and electromyographic activity evoked of abdominal muscles is measured (i.e. visceromotor response) [133-135] this test has been validated as painful in human subjects [137]. A number of insults to the bowel show enhanced visceromotor responses to colorectal distention. These include butyrate, hypertonic saline acidified with 2,4,6-trinitrobenzene sulfonic acid (TNBS), capsaicin, mustard oil, dextran sodium sulfate (DSS), and zymosan [18;35;42;49;58;61]. The insults are meant to mimic disease states such as irritable bowel syndrome (IBS) [29].

The genitourinary tract, modeling cystitis, is targeted with a number of noxious agents (VEGF, cyclophosphamide, bacterial infection, etc.) to injure the bladder. Evoked pain behaviors, visceromotor response to distension, or secondary hyperalgesia on the abdomen or paw is assessed [19;116;181].

3.8. Other models of disease

While this is a comprehensive review summarizing the most commonly used models, there are other models of disease that are also available that use standard reflexive and non-reflexive measures to assess pain and related symptoms. These include models of HIV-induced neuropathic pain [17;204;217], anti-retroviral neuropathy [90], sickle cell disease [25], and headache or migraine [47;92;121;157].

2.8. Summary

In summary, attempts have been made to model a number of human diseases. Many of these models have face validity, showing similar pathology and symptomology to the clinical condition. In designing experiments the appropriate choice of model is equally important to the outcome studied. The way pain is initiated and presents should reflect both the clinical presentation and the underlying disease mechanism, and should have predictive ability. Undoubtedly new models will continue to be developed as our knowledge of disease pathology progresses and more advanced techniques become available; however, such methods should be assessed according to the above criteria and validated for the conditions it is intended to model.

4.0. Conclusions

Developing and choosing the most appropriate experimental design for a study involves multiple factors, including the disease one is trying to mimic, the pain phenotype induced by the model, and the parameters evaluated by a given test. Having an understanding of the clinical condition will help in identifying the appropriate animal model and outcome measures. We suggest that, when examining new pain treatments, the disease model should most closely mimic the disease one is trying to model in humans. We further suggest that, since pain is a multidimensional experience, multiple behavioral outcomes should be used to gain a better understanding of the potential treatment's usefulness. Using measures of spontaneous pain, evoked pain, avoidance behaviors or quality of life/function will guide clinical usefulness of a given treatment. It is entirely possible that some treatments will have a greater effect on spontaneous pain but not evoked pain or vice-versa.

Quantitative sensory testing in human subjects measuring pain sensitivity of cutaneous and/or deep tissue shows predictive value for greater resting and movement-evoked post-operative pain [155]. Pressure pain thresholds over muscle are strongly correlated with

movement pain (pain with walking) in people with fibromyalgia [44]. Certain pain conditions such as postoperative pain might have significant resting pain but also have even greater evoked pain (particularly with movement), and thus using an animal model of postoperative pain that tests both spontaneous pain as well as evoked pain would be useful. On the other hand, people with osteoarthritis generally have minimal resting pain but significant pain with movement that reduces physical activity, as well as deep tissue hyperalgesia. Thus, measuring evoked deep tissue pain and effects on function may be more useful. Further, people with neuropathic pain and complex regional pain syndrome have significant spontaneous pain, cutaneous mechanical and thermal allodynia, and decreased function. Thus, measuring spontaneous pain, cutaneous mechanical and thermal allodynia and function would give greater insight into the treatment.

Differences in effects on outcome measures for clinical treatments have been found in animal models as well as in humans with experimental pain [98]. Having a greater understanding of the disease mechanisms in animals using a validated animal model of the clinical disease one is trying to model and multiple outcome measures should inform clinical translation. Clinical trials can then be more appropriately designed to test a variety of outcomes based on the animal data. In fact, modeling a battery of outcome measures in animals across the domains proposed through consensus for clinical trials by IMMPACT could prove valuable to enhance translation between basic and clinical research. Translation in pain research therefore must be two-way by modifying and adapting animal models and outcome measures as more pathology data on a clinical disease is discovered, and translating animal model and outcome measures to appropriate clinical pain conditions and measures.

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Table 1

Overview of reflexive and non-reflexive tests in different animal models of pain.

Reflexive Tests	Inflammatory	Neuropathic	Arthritic	Muscle	Cancer	Incision
Thermal						
Hot-Plate						
Hargreaves						
Cold						
Tail-Flick						
Acetone						
Mechanical						
Von Frey						

Reflexive Tests	**Inflammatory**	**Neuropathic**	**Arthritic**	**Muscle**	**Cancer**	**Incision**
Pressure						
Electrical						
Non- Reflexive Tests	**Inflammatory**	**Neuropathic**	**Arthritic**	**Muscle**	**Cancer**	**Incision**
Spontaneous						
Paw-Elevation/Licking						
Evoked						
CPP						
CPA						
Escape/Avoidance						

Reflexive Tests	Inflammatory	Neuropathic	Arthritic	Muscle	Cancer	Incision
Quality Of Life/Function	✓	✓	✓	✓	✓	