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Pain Research and Treatment: Policy Implications

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Abstract

Pain is a subjective experience for which we lack a thorough mechanistic understanding. While it has often been considered a secondary symptom of a disease, research has revealed that chronic pain can be recognized as a disease of its own. Preclinical studies often use animal models to understanding the pathology and test potential therapies with clinical trials of novel analgesics often showing underwhelming results. From a clinician's perspective, pain can be challenging to treat without incurring undesirable drug effects. Pain research, diagnosis, and treatment have changed dramatically over the last two decades. This has coincided with shifts in reliance on opioid-based approaches to managing pain. Here we present an overview of recent advances in preclinical research, novel approaches to diagnosis and treatment, along with considerations for animal care. Collectively, this report may provide a guide on which to base relevant policy changes that would meet the demands of societal need and satisfy the need for scientific evidence.

Keywords

pain, chronic pain, opioids, opiates, preclinical models, animal models, artificial intelligence, clinician education

Tweet

How has the field of pain changed when considering preclinical animal models, emerging technologies, clinician practices, and the patient population? @MaralTajerian and @Sebcredible weigh recent advances to consider how this field may shape policy nationally and internationally.

Key Points

- Preclinical animal models are essential for the progress of mechanism-based diagnosis and treatment of pain. However, analgesics identified in preclinical models do not effectively translate to clinical populations. A more inclusive consideration of animal models and the use of nonhuman primates should be supported. Additionally, encouraging federal funding agencies to limit a focus on opiate-based mechanisms and consider novel mechanisms of pain is merited.
- Chronic pain is challenging to diagnose due to it being a highly subjective experience for the patient. Success has been met when considering the subjective experience of patient, clinician education, and the collection of "big data" and integration with machine learning algorithms and artificial intelligence. While also important, the identification of novel biomarker panels is in their early stages of development.
- Pain treatment is often subject to trial-and-error pharmaceutical approaches that do not always target the underlying mechanism of pain pathology. This practice has led to an overreliance on opiates (and their unwanted effects) calling for better clinical practices and clinician education. This burden often falls on frontline primary care physicians that may have gaps in knowledge to recognize, address, and manage pain in their patients.
- Exploring mechanisms of pain in nonhuman animals provides a venue for improving animal welfare in research, veterinary, and commercial settings. The current inadequacy of standardized guidelines may overlook certain species and introduce confounds in the interpretation of research data. A broader, more inclusive consideration of models and defining pain beyond rodent/primate animals may provide an additional venue for understanding pain mechanisms and designing relevant therapies.

Introduction

Chronic pain is a significant health and socioeconomic problem affecting over 50 million adults in the United States alone (Yong et al., 2022). The last few decades have

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witnessed significant strides in the understanding of chronic pain, a topic of increasing interest to patients, researchers, clinicians, and policymakers. The evolving understanding of this complex disease necessitates a flexible outlook on the future of the field, guided by societal need and scientific evidence. Next, we present recent findings pertaining to pain research, diagnosis, and treatment, along with their implications to animal welfare that could guide policy changes both in the context of guidelines and legislation.

Preclinical and Clinical Studies of Pain

Most pain research is carried out in nonhuman subjects, with pain-free or pain patients being used to translate animal studies or when animal studies are not feasible or appropriate. While pain treatment is relevant to veterinary populations, the vast majority of pain studies in nonhuman animals are carried out for the purpose of modeling the human condition and the subsequent understanding of pain mechanisms and devising relevant interventions. Despite there being no standard guidelines or policies that regulate what animal can be used as a preclinical model for pain research, rodents remain the most-commonly used subjects, with varying success (Mogil et al., 2010). Funding institutions and scientific journals often emphasize rigor and reproducibility and may mandate that certain standards be met (inclusion of female animals, experimental design considerations such as blinding, availability of raw data, etc.) (Sadler et al., 2022). Indeed, one notable advance within the last decade has been the National Institutes of Health (NIH) expectation of including sex as a biological variable in research using vertebrate organisms (Miller et al., 2017).

Despite the encouraging results acquired in preclinical models, most clinical trials for analgesics have failed (Kissin, 2010), bringing to light the question of clinical validity of animal models due to large species differences in terms of biology and environment (Cho et al., 2021). The use of nonhuman primates may seem a way to increase model validity but carries significant ethical considerations. Instead of causing painful injuries in these animals for the purpose of research, it is possible to study naturally occurring pain such as osteoarthritis in rhesus monkeys (Abboud et al., 2021) and endometriosis in *cynmolgus* monkeys (Nishimoto-Kakiuchi et al., 2018) by means of tools and techniques adapted from those used in rodents. Examples from veterinary studies have been encouraging (Klinck et al., 2017). The translational gap may not be due to species differences alone and might instead reflect the complexity of pain sensation and perception. For example, the last two decades have witnessed an increased interest in voltage-gated sodium channel $NA_v1.7$ as a potential pain target based on data from human subjects and *in vitro* studies. However, to date, even potent NAv1.7 channel inhibitors have not shown analgesic efficacy in animal models and clinical trials (Eagles et al., 2022). There is therefore no "ideal" animal model for the study of pain. Instead, data from multimodal studies carried out in diverse organisms will inform the different stages of scientific inquiry.

Additional steps can increase clinical trial success. For example, to increase the probability of correctly predicting analgesic drug efficacy, the assessment of proof-of-concept mechanisms in addition to the common safety and tolerability measures would be useful (Cohen, 2010). For example, in a review of 121 early phase clinical trials of disease-modifying treatments in degenerative disorders, only 54% used mechanistic biomarkers to ascertain the engagement of the relevant drug target in humans (Vissers et al., 2021). Furthermore, to account for patient heterogeneity, recruitment strategies that employ community engagement may help increase clinical trial participation from under-represented groups (Gazaway et al., 2023). Finally, placebo-controlled trials may need to be revisited: data have shown increased placebo efficacy in U.S. analgesic trials (a phenomenon that parallels increased study length and size), which may result in failed clinical trials for novel analgesic agents (Tuttle et al., 2015). Drug efficacy is viewed as a measure relative to placebo, and increasing placebo efficacy may thereby diminish the relative drug efficacy and result in trial failure.

Despite the urgency of the chronic pain problem, research remains underfunded. Federal funding via the NIH has fortunately increased in the past few decades, but most of it is aimed at projects revolving around opiates (Agarwal et al., 2023), thereby curtailing more novel ideas. In addition to funding grants, the NIH also supports evidence-based workshops in topics such as pain and opioid therapies (Klabunde et al., 2023). These workshops play a key role in identifying gaps in research knowledge, assessing policy, informing clinical practice, and developing new guidelines, albeit with a strong emphasis on opiates. Such small investment in a complex medical problem with heavy disease burden is concerning for ethical and economic reasons. The issue becomes particularly urgent when considering global trends of increased research funding and scientific innovation outside of the US (Moses et al., 2015).

When pain research is funded outside of state or federal mechanisms, additional scrutiny is needed when research funders could potentially benefit financially from the scientific findings. This concern is not unique to pain research and can be evaluated throughout decades of studies funded by food and pharmaceutical entities. The influence of these industries on scientific research can be paramount and can include intentional and unintentional biases that favor said industries, and in a broader scope, influence research agenda and policy (Fabbri et al., 2018). A recent example comes from the cannabis industry where its legalization in many parts of North America has resulted in the allocation of cannabis-sponsored research positions across academic institutions and can serve as a case study in how industry sponsorship could shape research agenda (Grundy et al., 2023).

Diagnosis

Pain is a wholly subjective experience and has been historically neglected (Cohen et al., 2011) when thought to have psychological or socially motivated origins. For example, in the absence of a "frank" injury, it is possible to risk misdiagnosing pain despite patient reports. An additional concern is that chronic pain itself becomes confused as prolonged acute pain, despite the fact that acute and chronic phases of pain may differ in their mechanistic underpinnings. These clinical oversights may lead to neglect and may burden patients with stigma leading to co-morbidities such as anxiety and depression (Naushad et al., 2018), which further accentuate the subjective pain experience. For these reasons, emerging research that focuses on identifying, assessing, and quantifying pain has become essential. Advances in diagnostics have relied heavily on clinician–patient education, the identification of novel biomarkers, and the adoption of emerging technologies such as machine learning and artificial intelligence using patient data. Collectively, these efforts provide a tentative future with a personalized view of pain that can be subject to thoughtful planning and treatment.

Clinician–patient communication has led to a cultural shift in how clinicians consider patient reporting of pain (Whitten et al., 2005). Within this scope, the World Health Organization has recently expanded their international classification of disease and health-related problems (ICD-11) to elaborate on pain by itself or its connection with other underlying diseases. These considerations present opportunities to address pain comprehensively, for both clinician and the patient. For example, a multimodal assessment of pain prioritizes a qualitative pain narrative as the first step toward diagnosis and subsequent assessment of pain (Wideman et al., 2019). These diagnoses also consider psychiatric conditions such as depression and anxiety and how they contribute to chronic pain conditions. Clinician education on this front has also expanded into cultural awareness and sensitivity within patient populations. Different ethno-cultural identities generate variation in coping, emotional, and psychosocial states that shape pain perceptions. For example, locus of control or the perception success/failure rate due to internal/external variables is shaped by cultural beliefs which has been reflected in cultural variation in the perception of pain. An inclusive view of the various psychosocial variables that are tied to pain and subjective reporting of patient conditions will enable specialists and general practitioners with tools to work with patients in the treatment of their pain.

The emergence of big medical data and machine- or deep-learning algorithms also presents novel venues to diagnose pain (Matsangidou et al., 2021). These approaches provide diagnosis though the classification of clinical outcomes, manifestation of tentative symptoms, and the best course for effective pain management plans. The core of many of these approaches requires large datasets to train models that can present predictive frameworks for diagnostic potential. For example, medical measures, interventions, or recorded patient outcomes of pain present tractable datasets to predict pain intensity, identify the cause of pain, or how certain drugs can be effectively dosed. These data can be derived from clinical reports, medical imaging or electrophysiological measurements. Effectively, healthcare providers and insurance providers will be motivated to leverage biomedical big data to build models that will drive down the cost of personalized medicine and provide an objective diagnosis of a subjective condition.

Outside of using just-mentioned clinical data is the potential for diagnostic tools derived from computer vision and noninvasive measures of real-time patient behaviors. For example, posture estimation provides an emerging venue to recognize different modalities of pain in preclinical models of pain as well as in clinical subpopulations. Preclinical models of neuropathic and inflammatory pain have been validated to reveal subtle changes in gait with analgesics in simple motor tasks (Xu et al., 2019). In humans, this effort has allowed the use of software that can track movement and estimate posture, thereby providing a comprehensive understanding of gait. Applications of this technology have led to classifiers that can detect knee arthritis and limited movement (Lv et al., 2022). The use of computer vision and artificial intelligence has also been rigorously applied to animal models with a focus on classifiers that measure pain from facial reactions. For example, a coded grimace scale in mice for pain (Langford et al., 2010) can be curated for machine learning models allowing automated the assessment of pain (Tuttle et al., 2018). These studies are currently being translated within the clinic and focus on building classifiers for the "pain face" using critically ill patients living with chronic pain (Wu et al., 2022) and ongoing trials (See Pain Assessment in Cancer Patients by Machine Learning (PASCALE)). Similar approaches have also been applied to patient voice to detect phonic traits such as increased pitch and loudness that can be indicative of pain (Borna et al., 2023). At this point, their predictive potential is limited to their training dataset. Limited generalizability of any model can arise from biased training sets leading to issues such as racial discrimination (Obermeyer et al., 2019). These models often present a black box that, while predictive, lacks mechanistic understanding of pain conditions.

Lastly, the identification of novel biomarkers for pain can offer a complementary toolset to subjective self-reporting. In a recent retrospective observational report (Gunn et al., 2020), biochemical measures collected in the clinic were associated with chronic pain that include elevated levels or certain compounds (quinolinic acid, pyroglutamate, xanthurenic acid, acrolein) along with abnormally low neurotransmitter metabolites. However, each of these measures was observed only within a subset 10–29% of patient populations, suggesting an unmet need with current clinically attainable biomarkers. Due to the heterogeneous modalities associated with chronic pain, the pain research community considers that no single biomarker can comprehensively define all types of pain (Eldabe et al., 2022). This has led to a valuation of integrative composite panels that associate with certain modalities of chronic pain. Assessing biomarkers presents a range of feasibility limited by cost and invasiveness of test. For example, studying urine metabolites is far easier than carrying out a spinal tap for cerebrospinal fluid or an fMRI. Similarly, the study of these tissues can have a range of depth in their metabolomic analysis (Patti et al., 2012), gene expression patterns (Niculescu et al., 2019), or how genes are regulated (Massart et al., 2016). Note, however, that many of these approaches are in an investigative and exploratory stage.

Treatment

Once pain is diagnosed, it is mainly treated with an array of pharmaceuticals, starting with those with the mildest side-effects and progressing to meet the demand for satisfactory pain relief. As this approach does not target the mechanisms behind the experience of pain, this "trial and error" tactic may leave both patient and physician frustrated. For example, opiates continue to be poised as the gold standard in managing moderate to severe pain, but they are globally associated with unwanted outcomes, particularly when used in suboptimal contexts (for example, in certain acute pain scenarios). These could include prescriptions following surgical intervention or acute pain episodes, with the need to develop best-practice strategies (Yorkgitis and Brat, 2018). In particular, opioid prescribing policies need to be clear and well-studied, because the misapplication of current opioid prescribing policies may result in unintended consequences such as addiction and other side-effects (Maierhofer et al., 2023). Patient views reflect these facts as they remain cognizant of the risks of opioid-use disorder (Bulls et al., 2023). Implementing opioid stewardship may improve their use in pain management and may reduce opioid-related morbidity and mortality. Efforts are underway to reach a universally accepted definition (Shrestha et al., 2023).

The need for novel pain therapies with more favorable profiles is clear. For example, cannabis use has been increasingly legalized and accepted, with evidence showing its viable role in chronic pain treatment (Bobitt et al., 2023). Additionally, the last few decades have seen a renewed interest in psychedelic medicines, particularly as they apply to chronic pain. Preliminary research is promising, with evidence suggesting efficacy in treating pain and improving quality of life, although more data are needed before these compounds could be approved by regulatory bodies (Zia et al., 2023). Furthermore, a slew of policy changes should be implemented to ensure equitable access to these classes of drugs.

Primary care physicians, who are the main providers of pain relief for non-cancer pain patients, report a multitude of challenges including gaps in knowledge and skills required for the assessment, diagnosis, and treatment of pain, tapering high-dose opioid plans, and limited access to pain specialists (McEwen et al., 2023). These challenges are accentuated when taking into account the heterogeneity of the patient population in terms of age, socioeconomic and cultural factors, race and ethnicity, etc., thus highlighting the need to prevent the marginalization of minoritized groups. For example, youth suffering from chronic pain may lack the necessary health literacy and self-management skills (Brown et al., 2023). Similarly, caregivers of older adults with pain often are not given the necessary information to successfully manage the care regimen of their family members (Horgas et al., 2022). Globally, low income countries may not prioritize chronic pain, and thus express, specific pain policies may be absent (Briggs et al., 2023) while the United States has overtaken European countries in the severity of the opioid epidemic (Gomes et al., 2018). Countries are becoming increasingly diverse in terms of racial and ethnic makeup, prompting the need for medical pluralism in the context of health policy (de-Graft Aikins et al., 2023).

Of utmost relevance to policy discussions is the efficacy of supplied treatment. In the context of pain, novel approaches that go past traditional efficacy trials may be needed. For example, pragmatic trials that consider a more comprehensive set of external validity questions critical for patients, clinicians, and policy makers may prove useful (Hohenschurz-Schmidt et al., 2023). The use of real-world data, or health data that is routinely collected for research purposes, is another novel approach. A systematic review of this methodology demonstrates that, if rigorous quality standards are met, this approach can be valuable in generating high-quality evidence that goes beyond clinical trials (Vollert et al., 2023). Finally, emerging technologies such as machine learning can help construct prognostic profiles (Zmudzki and Smeets, 2023) and therefore aid in treatment personalization and outcome optimization.

The design of a satisfactory treatment plan does not ensure its implementation, with social and financial restraints being the main culprits. A recent study examining a decade of insurance claims data found that high-deductible plans are associated with a reduced probability of pain treatment, with nonpharmacological therapies being the most affected. Keeping in mind that high-deductible health plans capture a significant share of the healthcare market, there is a risk that efficacious and multimodal therapies may be underused (Kennedy-Hendricks et al., 2023). Conversely, when complementary and integrative health approaches were offered via the Veterans Health Administration, their use grew significantly (Taylor et al., 2023). These studies highlight the need for revising federal and state health policy to accommodate these more holistic therapeutic approaches in patient care.

Animal Care Implications

Pain and discomfort are main considerations for animal welfare policy in research, commercial, and entertainment settings (Simmonds, 2018). As the majority of preclinical research subjects are rodents, there are multiple guidelines regarding their care and use across the globe with ongoing efforts to categorize and quantify experimental processes, with particular emphasis on the minimization of pain and distress (for example, see Tappe-Theodor et al., 2022). Despite scientific journals routinely including statements attesting to the compliance of the animal studies with international regulations, there are often discrepancies in their implementation and an apparent lack of oversight (Diaz, 2020). The inability/unwillingness to sufficiently treat pain in research animals is not solely an animal welfare problem but can be a significant confound influencing data replicability and reproducibility. A recent review reports that current publication guidelines fail to appreciate how pain or its treatment may affect the acquired data, thereby casting doubt on the validity of published data where experiments rely on animals undergoing painful procedures (Carbone and Austin, 2016). Finally, pain researchers are uniquely challenged by these considerations because they need to abide by animal care guidelines while inducing pain in experimental models in order to study it.

These points are doubly significant when working with most invertebrate organisms. While working with vertebrate and "higher" invertebrate (octopus, squid, crayfish, etc.) animals involves ethics approval protocols corresponding to the perceived level of "complexity" of the organism, there are often no specific guidelines for "lower" invertebrate subjects. This is mainly due to ongoing debates regarding which animals can feel pain, an issue that is reliant on biology as much as it is on the definition of pain. Regardless, emerging evidence suggests the presence of pain in cephalopods and efforts are underway to identify analgesic and anesthetic targets that could be used to improve their welfare (Deutsch et al., 2023). Similarly, a recent review of over 300 studies discovered that, at least in six major insect groups, reliable data support pain perception (Crump et al., 2023).

Evidence of analegesis, either via endogenous systems or exogenous application of pharmacological agents (anesthetics, anxiolytics, antidepressants, etc.), is often used as a criterion to establish the presence of pain in animals. Since most of preclinical pain research is carried out in model organisms (mice, rats, nonhuman primates), there is very little that is known about analgesic efficacy in nonmodel organisms. As such, the lack of human-like endogenous and exogenous analgesic efficacy simply indicates that those same mechanisms may not be present in all species, and not that those species do not experience pain. For example, injured honeybees did not "choose" to increased self-administration of opioids (Groening et al., 2017), which could erroneously be presented as evidence against pain in insects, despite the fact that insects lack opioid receptors.

Unlike the context of preclinical research, where animal subjects are seen as vehicles to study human pathology, veterinary medicine research aims at studying and treating the animals themselves. In the assessment and management of pain, multiple, general, or species-specific guidelines are available, many reporting the under-recognition of pain in animals (Steagall et al., 2022).

Animal welfare in commercial and entertainment sectors is often viewed within the contexts of profitability, feasibility, and ethics, with the understanding that welfare considerations may differ between those taking care of the animals and those being entertained by the animals (Veasey, 2022). Understanding pain in animals is important for ethical reasons, and animal welfare policy implementation can aid in instilling public trust in science as well as protecting animals in commercial and entertainment sectors.

Conclusions

Policy guidelines must be informed by research logistics, healthcare infrastructure, and reliable preclinical and clinical data, with the understanding that policies need to be constantly revisited, refined, and re-designed to accommodate the changing needs of the clinic and to correct the oversights of prior policy. Despite best intentions, U.S. state policies only modestly reduced opioid overdose mortality (Buonora et al., 2022) highlighting the complexity of the required framework that must go beyond the patient–clinician unit.

Perhaps a common thread that ties together the points discussed here is the subjective nature of pain perception that makes it difficult to define, diagnose, treat, and extend to nonhuman subjects. With ongoing advances in pain research and its underlying mechanisms (Robert et al., 2010), perhaps science will be able to provide a reliable physical substrate that can be objectively quantified across species.

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