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Mini-review

An industry perspective on the role and utility of animal models of pain in drug discovery

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HIGHLIGHTS

- Evidence that new pain drug discovery failures are due to insufficient efficacy is poorly documented.
- Discovery of new drugs requires data from many assays in addition to behavioral models.
- Pain models are used in drug discovery to rank order compounds and focus resources.
- Use of new pain models/endpoints to improve translational success first requires their validation.
- Pain model data analysis using effect size and NNT may create better alignment with clinical data.

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ABSTRACT

In recent years, animal behavioral models, particularly those used in pain research, have been increasingly scrutinized and criticized for their role in the poor translation of novel pharmacotherapies for chronic pain. This article addresses the use of animal models of pain from the perspective of industrial drug discovery research. It highlights how, when, and why animal models of pain are used as one of the many experimental tools used to gain better understanding of target mechanisms and rank-order compounds in the iterative process of establishing structure–activity relationships (SAR). Together, these models help create an 'analgesic signature' for a compound and inform the indications most likely to yield success in clinical trials. In addition, the authors discuss some often under-appreciated aspects of currently used (traditional) animal models of pain, including how industry balances efficacy with side effect measures as part of the overall conclusion of efficacy. This is provided to add perspective regarding current efforts to develop new models and endpoints both in rodents and larger animal species as well as assess cognitive and/or affective aspects of pain. Finally, the authors suggest ways in which efficacy evaluation in animal models of pain, whether traditional or new, might better align with clinical standards of analysis, citing examples where applying effect size and NNT estimations to animal model data suggest that the efficacy bar often may be set too low preclinically to allow successful translation to the clinical setting

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1. Introduction

Discovering and developing novel drugs for use in humans is arduous. Obstacles are present at many levels, including biology, chemistry, intellectual property, and regulatory considerations. When pursuing unprecedented targets, these obstacles are associated with even greater risk. As such, only a fraction of preclinical effort will translate to successful clinical studies, a challenge for drug discovery in any therapeutic arena. Although pharmacokinetic parameters were once a main reason for clinical development failures, this is no longer the case [19]. In recent years, criticism has been widely levied against the animal models used in research and development, and specifically regarding the predictive utility of animal models of pain [4,23,27,40]. The widespread belief that these models have limited or no translational value comes from both academia and industry, with many suggesting that the paucity of new analgesic drugs results from animal model data that are misleading in their conclusion of efficacy and/or poorly reflect clinical pain signs and symptoms [3,33,43]. With that said, it is the authors' firm belief that the current translational challenges should not in any way lessen the value of, or confidence in, animal models of pain.

Drug development efforts fail for numerous reasons: toxicity, dose-limiting side effects, failure to show improvement or otherwise differentiate versus standard of care (SOC) drugs, or poor selection of indication or patient cohort, among others. While a few examples exist where efficacy demonstrated in animal models of pain has failed to translate to clinical efficacy [11,13,28], in general, such failures have been poorly documented with little published data. Thus, definitive conclusion that animal models yield 'false positive' data is not clearly supported. Likewise, it is all-but certain the converse has never been tested, namely identification of a 'false negative' through clinical trial of a mechanism that failed to show efficacy preclinically. In this light, it is worth noting that there have been successes in translating preclinical efficacy to the clinic, including the approval of ziconitide, the still-evolving tanezumab story, and the more recently published successful trial of a TRPV1 antagonist compound, albeit in the context of third molar extraction [32]; whether TRPV1 antagonist compounds prove efficacious in more complex, chronic pain conditions awaits data from further clinical pain studies. In this article, the authors put forward a current industry perspective on existing, 'traditional' models of pain as well as new models being developed. We offer a rationale for how animal models are used across the drug discovery process, one that may differ in some notable aspects from their use in academic research. While recognizing the limitations of these models, we hope to highlight some of the current misconceptions around animal models of pain and suggest for consideration potential improvements.

2. Current status and new developments in animal models of pain

Numerous animal models of pain have been designed as a means to investigate mechanisms underlying nociceptive, inflammatory, and nerve injury pain. It is beyond the scope and intent of this paper to describe these models, their methodology, variations, and endpoints, but the reader is directed to reviews by Mogil [25] as well as Joshi and Honore [17] for more details. Most models couple a method for inducing a hypersensitive state (the model) such as mechanical trauma or injection of an algogenic substance to a behavioral assessment (the endpoint). Endpoints traditionally include either direct observation of non-evoked, spontaneous behaviors such as flinching, licking, biting or altered weight-bearing, or evoked responses such as paw withdrawal, vocalization or struggle following application of a stimulus (heat, blunt pressure, focused tactile probing, etc.). These behaviors are believed to represent pain being experienced by the animal and have been referred to as "pain stimulated" [38]. Advances are being made in establishing disease models to represent osteoarthritis, fibromyalgia, post-operative, visceral, and thermal injury pain, among others. Likewise, the methodology for developing new endpoints is growing and now includes an array of measures such as electroencephalograms [10], alterations in sleep [22,37], movement (thigmotaxis) [12] or gait [30], changes in social or 'well-being' behaviors such as burrowing [1], and choice (preference, aversion) paradigms [14,18,39,41], intracranial self-stimulation and other pain-depressed behaviors [26,29], even facial expressions [20]. It is safe to say that hundreds of model/endpoint combinations are now possible and being described in the literature.

Interest has also grown in the development and implementation of large animal and/or naturally developing ('naturalistic') models of pain based on the assumption these will show greater face, construct and, ultimately, predictive validity. There is support for the view that new models utilizing novel endpoints are needed in order to overcome the current translational impasse in the development of novel pain drugs [20,23]. A number of academic and industrial groups are accelerating efforts around, for example, dog models of arthritis and nonhuman primate models of inflammatory or nerve injury pain. Although these models ultimately may reveal insights into pain behaviors not readily apparent in rodents and provide translational benefits from both pharmacokinetic/pharmacodynamic (PK/PD) and toxicology perspectives, they also present a number of challenges, not the least of which relates to greater heterogeneity in the manifestations of 'spontaneous' pain relative to that induced in rodents by directed means. While rodent models utilizing homogeneous age, sex, weight, and strain are criticized as not being representative of clinical pain, naturalistic models in larger animals make establishing robust endpoints and reproducibility between experiments much more difficult, even if they may more closely mimic human-like disease heterogeneity. Power calculations for compound assessments in a typical behavioral study over a 3-point (½ log) dose response typically suggest group sizes of 8–10 animals; including positive and negative control groups, this approaches a total experiment size of 50 animals, a number not feasible when using larger animals. In addition, because injury and, hence, pain severity is not controlled as it is when applying a uniform insult to groups of rodents, intra- and inter-group variability is likely to obscure conclusions of statistical efficacy. Assays using thermal or mechanical stimuli to evoke nocifensive responses in large animal models of pain are the same as those criticized for use in rodent models. Unfortunately, measurement of non-evoked pain endpoints in larger species is still rudimentary and highly variable, although advances are being made [5,44]. The caution is to maintain perspective regarding the fact that animal models, even those utilizing non-human primates, represent, at best, only an approximation of human biology and behavior. In an almost paradoxical way, many, while acknowledging this gap, remain keen to anthropomorphize animal behavior.

Efforts to generate new behavioral data, particularly those revealing insights into cognitive and affective aspects of pain, are certain to enrich our understanding of pain pathobiology and may ultimately increase translational success; however, in our view, there are other gaps in the translational chain more readily accessible and likely to yield positive results in the short term. These include better patient phenotyping and stratification, implementation of trial designs that may help minimize placebo effects, and, in the preclinical realm, setting the bar higher with respect to what is viewed as efficacious enough to merit advancement into development (discussed below).

Gaining confidence in the predictive validity of any behavioral assessment is a lengthy process. Ideally, compounds proven