Comprehensive Review

PAIN

Translational pain assessment: could natural animal models be the missing link?

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Abstract

Failure of analgesic drugs in clinical development is common. Along with the current "reproducibility crisis" in pain research, this has led some to question the use of animal models. Experimental models tend to comprise genetically homogeneous groups of young, male rodents in restricted and unvarying environments, and pain-producing assays that may not closely mimic the natural condition of interest. In addition, typical experimental outcome measures using thresholds or latencies for withdrawal may not adequately reflect clinical pain phenomena pertinent to human patients. It has been suggested that naturally occurring disease in veterinary patients may provide more valid models for the study of painful disease. Many painful conditions in animals resemble those in people. Like humans, veterinary patients are genetically diverse, often live to old age, and enjoy a complex environment, often the same as their owners. There is increasing interest in the development and validation of outcome measures for detecting pain in veterinary patients; these include objective (eg, locomotor activity monitoring, kinetic evaluation, quantitative sensory testing, and bioimaging) and subjective (eg, pain scales and quality of life scales) measures. Veterinary subject diversity, pathophysiological similarities to humans, and diverse outcome measures could yield better generalizability of findings and improved translation potential, potentially benefiting both humans and animals. The Comparative Oncology Trial Consortium in dogs has paved the way for translational research, surmounting the challenges inherent in veterinary clinical trials. This review describes numerous conditions similarly applicable to pain research, with potential mutual benefits for human and veterinary clinicians, and their respective patients.

Keywords: Preclinical animal models, Natural, Experimental, Validity, Applicability, Translation

1. Introduction

Major goals of pain research are improving our understanding of pain pathology and identifying novel molecular therapeutic targets for better clinical pain management. Despite huge scientific and technological advances, and tremendously increased research and development costs, drugs are more likely to fail in clinical development today than they were in the 1970s.[15,134] The credibility of efficacy data obtained from animal disease models has lately been called into question, in biomedical research in general[88,134,148] and in the pain field specifically.[14,93-95,121,142] Scientific research also faces a "reproducibility crisis," which may be a contributing factor in the translational crisis. Failure rates in the clinical phase are around 90% to 95%,[8,59,122] due in part to the challenges of interpreting animal model data. The predictability of basic research varies depending on the understanding and complexity of disease biology, whereas for therapeutics targeting infectious diseases, success rates are high, for diseases involving complex mechanisms, such as neurological diseases and cancer, they can be as low as 2.3%.[59] For pain studies, the likelihood of eventual FDA approval of a drug entering phase I studies has been reported at 10.7%.[59] Some have blamed animal models for these translational difficulties. Indeed, a lack of tangible benefit over a long enough period of time could lead one to question both the commitment of substantial funding to, and the ethics of, animal use for this research.[121,148] However, the lack of success is almost certainly also associated with other factors, and both the initial compound development and in vitro screening programs should be examined, as well as the animal models used.

The main challenges of animal models are not only recreating disease conditions but also defining measurable and clinically translatable efficacy parameters. For a pain model to be valid, it should encompass key elements of the human pain experience and measure the pertinent aspects of that experience. Given that an animal model consists of a subject, a method of pain induction (ie, an assay), and an outcome measure(s),[93] each of these components should reflect, as closely as possible, the clinical

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PAIN 158 (2017) 1633-1646

http://dx.doi.org/10.1097/j.pain.0000000000000978