HHS Public Access

Author manuscript

Anesthesiology. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Anesthesiology. 2016 November ; 125(5): 846–849. doi:10.1097/ALN.0000000000001340.

Preclinical Pain Research: Can we do Better?

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Abstract

Regrettably, the list of unique analgesic tools has expanded very slowly over the past few decades. Many very promising drugs have failed once tested in clinical populations, and the associated costs of these translational failures have been extremely high. Part of this problem can be traced to the ways we select and use preclinical tools and perhaps in the way we report our findings. We are beginning to reevaluate our selection of animal models and the methods we use to measure pain-related responses in these animals. In addition, many journals now require a clear statement of the experimental hypothesis, the details of the experimental methods, a description of the statistical approach to analyzing the data and the disclosure of conflicts of interest. These new practices pose challenges to laboratory-based research groups. However, a more rigorous approach to preclinical investigations may be necessary for the successful development of new analgesics.

That we have a limited ability to control both acute and chronic pain is clear. With respect to acute pain, one recent survey suggested that >60% of patients experience moderate to extreme levels of pain postoperatively despite the creative use of our existing armory of analgesics[1]. This figure has changed little in more than 10 years[2]. Acute pain, of course, is not the only problem; approximately 25% of the US population suffers from chronic pain, a problem costing the economy hundreds of billions of dollars annually[3]. Moreover, the overzealous use of our most powerful class of analgesics, the opioids, has spurred an epidemic in prescription opioid overdose as reported by the Centers for Disease Control[4]. Looking more closely at the situation reveals that most treatments for pain including analgesics, injections, devices, complementary approaches, etc. are fundamentally similar to ones we have used for decades (or in the case of some complementary approaches, centuries).

How could this be? Pain research is a robust and diverse field. The scientific literature is replete with compelling reports from laboratories around the world describing the cellular and molecular details of signaling mechanisms, neuroplastic changes occurring after tissue injury, alterations in the functioning of glial cells and many other pain-related phenomena.

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Conflicts of interest: The author declares no competing interests.

In preclinical models newly designed drugs have been impressively effective in changing pain-related behaviors. Unfortunately, clinical trials using these same drugs have most often failed, and the costs of analgesic development are substantially higher than for many other types of medications[5]. The number of companies pursuing analgesic development has therefore dwindled in recent years.

Pain research now finds itself at a crossroads; what went wrong and how can we do better? This question has been the focus of several recent publications[6,7], and has been a featured topic at pain research meetings[8]. The themes emerging from this soul searching fall into three basic arenas: poor animal models, poor pain measures and poor reporting practices[9–12]. We need to up our game!

Poor preclinical pain models

Why do we use the models that we do? For example, diabetic neuropathy and radiculopathy are two of the most common types of neuropathic pain seen clinically, but much of our animal work focuses on nerve injury models, typically involving partial ligation of the sciatic nerve or its distal branches, with the implicit assumption that the observations made will be generalizable and translatable. This has not worked out very well. Similarly, there exist a host of commonly used models involving the subcutaneous injection of noxious substances, e.g. formalin, carrageenan, capsaicin, etc., said to mimic inflammatory pain such as accompanies rheumatoid arthritis or surgical incision with similar difficulties experienced in translation. For example, while it is clear that inflammation accompanies incision, it has been clearly shown that drugs effective in reducing responses in simple inflammatory models are not always effective in incisional models involving the disruption of skin, muscle and connective tissue[13]. A potential problem represented in these examples is face validity – the models selected should resemble the conditions they are intended to inform. Moreover, most studies use single models although it is seldom clear why one model was selected over another that could provide very different results. Another problem involves the time courses we often study; does it make sense to study nerve injury days after surgery when clinical neuropathic pain often involves pain experienced months to years after the presumed inciting events? And what about the inclusion of biological and psychological variables known to affect clinical pain and analgesic responsiveness including sex differences, ages, genetic backgrounds, stress, sleep disturbance, etc.? Shouldn’t these variables be explored in laboratory pain models before attempting to translate experimentation to human subjects? Finally, there is the thorny issue of basic differences in neurophysiology. The failure of agents effective in rodents to translate to humans suggests that the chemistry and wiring of pain in humans may be different from these laboratory animals in fundamental ways.

These problems are difficult, but perhaps not insurmountable. Although the idea that models with higher apparent face validity will provide more readily translatable results is itself a hypothesis, we do have models more closely resembling their targeted clinical conditions than many in common use. For example, several types of joint inflammation models are available in which to study arthritis that are sometimes used in parallel in the same overall project to bolster confidence in the results[14]. Complex regional pain syndrome (CRPS) can be modeled by creating the same circumstances in animals that lead to many cases of CRPS

appearing in our clinics: distal limb fracture followed by immobilization[15]. Chemotherapy induced neuropathy, diabetic neuropathy, post-surgical pain and other common types of pain all have multiple models available for laboratory use, but they are often passed over in favor of ones that are simpler or more popular.

Once a model is selected, we have the technical capabilities to study the animals under a broad array of conditions relevant to clinical pain. For example, we are able to age animals prior to injury, follow cohorts for months rather than days, induce stress, deprive of sleep, control exercise levels, etc. This is fortunate since funding organizations including the National Institutes of Health (NIH) have adopted guidelines and requirements for the representation of biological diversity and common comorbidities in preclinical work they support. We also have available various approaches to the problem of studying pain in single strains of laboratory animals. Dozens of strains of rats and mice are available in which to determine the robustness of an investigator's findings. Beyond the use of rodents, we have large animal models of many common types of pain including ones involving dogs, sheep, pigs, horses and primates[12]. Some of these species naturally develop conditions similar to those we wish to study in humans, e.g. osteoarthritis and cancer, or undergo surgery, and investigators are beginning to use these animals in preclinical analgesic development[16,17]. It is hoped, but remains to be demonstrated, that the basic pain-related pathology, neurophysiology, pharmacokinetics and pharmacodynamics in these alternative species provide translational advantages over rodents.

Poor preclinical pain measures

Why do we use the measures that we do? Pain is an experience we cannot directly measure in laboratory animals although some investigators regularly use the term "pain" when interpreting behaviors in rodents. Therefore, we focus on nociception, a term related to the processing of information related to the application of a noxious stimulus. Most commonly noxious heat or mechanical stimulation is applied to a rodent's paw in order to evoke a response. These evoked responses largely involve spinal reflexes. They are rapid, reproducible and inexpensive to use. Unfortunately, thermal hyperalgesia and mechanical allodynia are often not the sole drivers of a patient's pain complaints. For example, cross-sectional data from a group of 1236 neuropathic pain patients found mechanical allodynia in only about 20% of the cohort and many had sensory loss rather than gain[18]. In addition, a recent study involving patients with complex regional pain syndrome demonstrated that anti-hyperealgesic responses to medications correlate poorly with reductions in clinical pain scores[19]. Relatedly, we have reached the consensus that in clinical trials in order to understand the therapeutic potential of candidate analgesics, outcomes should include changes in emotional status and functional capabilities, e.g. IMMPACT guidelines[20]. Seldom do our animal studies attempt to address these endpoints.

Fortunately, there are many alternatives to evoked responses involving hopefully more informative behaviors. One group involves the animal's "body language." These measures include the automated analysis of spontaneous flinching, guarding, changes in facial expression, alterations in weight bearing on injured limbs, ultrasonic vocalization and other endpoints. More sophisticated analyses involve conditioned place preference paradigms and

various types of operant assays applicable to pain and analgesic testing. These assays probe the tonic aversive nature of a stimulus and the effects of injuries and drugs on an animal's affective state. In some cases, these experiments have led to conclusions different from those obtained using simpler reflexive assays[21,22] although comprehensive comparisons of results obtained when using evoked versus spontaneous measures have not been reported. Likewise, techniques to assess anxiety and depression-like states, cognitive status and physical functions such as gait and balance are available for rodents and larger species.

Poor reporting practices

Do our scientific reports contain clear and accurate descriptions of the work as it was conducted? At this point it is well-recognized that the reproducibility of preclinical research, not just that related to pain, is alarmingly low. Several retrospective analyses have suggested that for less than 50% of published preclinical studies can the results be fully reproduced, and this generates more than $28 billion in wasted effort in the US alone each year[23]. Problems related to study design, data analysis and laboratory protocols have been identified as major contributors to the reproducibility problem emphasizing the need for reports to be clearly and accurately written, for all key experimental details to be included, and for sources of potential bias to be disclosed.

Observations such as this have led to the development of reporting guidelines including ARRIVE – Animals in Research: Reporting In Vivo Experiments[24], and the more specifically pain-related guidelines from the Preclinical Pain Research Consortium for Investigating Safety and Efficacy (PPRECISE) group[9]. Key requirements of the ARRIVE checklist for authors include a clear statement of the guiding hypothesis, well-described methods, descriptions of observational blinding procedures, details of statistical methods, transparency concerning sources of support and other factors. Such guidelines may encourage better scientific practices and facilitate the reproduction of results, the foundation upon which scientific progress and ultimately successful clinical translation rely.

What we might do differently

Moving forward there is probably a need to define expectations for preclinical pain research projects and reports. It is suggested that we begin with what admittedly might be seen as an over simplification – laboratory projects should either be considered mechanistic or pre-translational. Mechanistic or "discovery" projects could be viewed as refined versions of today's better reports. The hypotheses should involve the exploration of novel biological concepts rather than incrementally different questions. The techniques should be highly robust, contemporary and designed to test the central hypothesis from various angles. The project should follow a pathway or explore a mechanism in sufficient detail that our understanding of the relevant area of biology is improved fundamentally by the data. In this type of project, it would be permissible for the model to be simple and the outcomes narrow if that allows the biological process to be studied rigorously. In contradistinction, pre-translational projects would be expected to generate data upon which an early phase clinical trial could be based. They would use one or more well-validated models. Both sexes of animals would be assessed for key endpoints along with biological and environmental

variables important to the treatment of pain. Investigators might chose to employ multiple strains of the same species of animal or use different species. The intervention, e.g. use of a novel drug, might be conceptually simple, but rigorous pharmacological testing and the assessment of a panel of pain-related outcomes would be expected, e.g. nociceptive sensitization, the intensity of a tonic aversive state, anxiety-like behaviors, cognitive function, gait, etc.

It will not be easy to change our approach to preclinical pain research. I admit that my own laboratory program does not always pursue its investigations as outlined in the preceding paragraphs. In fact, a major obstacle to advancement is that we do not know which new models and tests will provide additional translational value, and which will simply add unnecessary effort. This issue itself should be the subject of careful investigation. Additional barriers include the costs of retooling laboratories to conduct more sophisticated tests, the time required to fully validate new experimental procedures and the effort required to retrain investigators and staff regarding new experimental and reporting standards. Indeed, departments, review groups and funding agencies will need to focus less on numbers of papers when judging productivity and more on the structure and potential impact of the work completed. Such expectations for preclinical research raise the bar significantly. On the other hand, if our goal is to hasten the availability of much needed analgesic therapies, these are changes we need to make.

Acknowledgments

Statement of support: Support was provided by the Department of Veterans Affairs grant I01RX001475 and the National Institutes of Health grant NS072143 to JDC.

References

1. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014; 30:149–60. [PubMed: 24237004]
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003; 97:534–40. table of contents. [PubMed: 12873949]
3. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): 2011.
4. Centers for Disease C, Prevention. CDC grand rounds: prescription drug overdoses – a U.S. epidemic. MMWR Morb Mortal Wkly Rep. 2012; 61:10–3. [PubMed: 22237030]
5. Sertkaya A, Wong HH, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clin Trials. 2016; 13:117–26. [PubMed: 26908540]
6. Mao J. Current challenges in translational pain research. Trends Pharmacol Sci. 2012; 33:568–73. [PubMed: 22959652]
7. Woolf CJ. Overcoming obstacles to developing new analgesics. Nat Med. 2010; 16:1241–7. [PubMed: 20948534]
8. Sutherland S. APS Basic Science Shared Interest Group Dinner and Town Hall Discussion: Animal Models and Testing in Preclinical Pain Research Pain Research Forum. 2016
9. Andrews NA, Latremoliere A, Basbaum AI, Mogil JS, Porreca F, Rice AS, Woolf CJ, Currie GL, Dworkin RH, Eisenach JC, Evans S, Gewandter JS, Gover TD, Handwerker H, Huang W, Iyengar S, Jensen MP, Kennedy JD, Lee N, Levine J, Lidster K, Machin I, McDermott MP, McMahon SB, Price TJ, Ross SE, Scherrer G, Seal RP, Sena ES, Silva E, Stone L, Svensson CI, Turk DC,

Whiteside G. Ensuring transparency and minimization of methodologic bias in preclinical pain research: PPRECISE considerations. Pain. 2016; 157:901–9. [PubMed: 26683237]

10. Barrett JE. The pain of pain: challenges of animal behavior models. Eur J Pharmacol. 2015; 753:183–90. [PubMed: 25583180]
11. Berge OG. Predictive validity of behavioural animal models for chronic pain. Br J Pharmacol. 2011; 164:1195–206. [PubMed: 21371010]
12. Henze, DA., Urban, MO. Large Animal Models for Pain Therapeutic Development, Translational Pain Research: From Mouse to Man. Kruger, L., Light, AR., editors. Boca Raton, FL: 2010.
13. Zahn PK, Brennan TJ. Lack of effect of intrathecally administered N-methyl-D-aspartate receptor antagonists in a rat model for postoperative pain. Anesthesiology. 1998; 88:143–56. [PubMed: 9447867]
14. Malfait AM, Little CB. On the predictive utility of animal models of osteoarthritis. Arthritis Res Ther. 2015; 17:225. [PubMed: 26364707]
15. Guo TZ, Offley SC, Boyd EA, Jacobs CR, Kingery WS. Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. Pain. 2004; 108:95–107. [PubMed: 15109512]
16. Brown DC, Agnello K, Iadarola MJ. Intrathecal resiniferatoxin in a dog model: efficacy in bone cancer pain. Pain. 2015; 156:1018–24. [PubMed: 25659068]
17. Castel D, Naveh M, Aharon A, Doron O, Meilin S. Prolonged Analgesic Effect of PRF-108 and PRF-110 on Post-operative Pain in Pigs. Pain Ther. 2016; 5:29–42. [PubMed: 26724813]
18. Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, Gierthmuhlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihofner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uceyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010; 150:439–50. [PubMed: 20627413]
19. Rauck RL, North J, Eisenach JC. Intrathecal clonidine and adenosine: effects on pain and sensory processing in patients with chronic regional pain syndrome. Pain. 2015; 156:88–95. [PubMed: 25599305]
20. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003; 106:337–45. [PubMed: 14659516]
21. King T, Vera-Portocarrero L, Gutierrez T, Vanderah TW, Dussor G, Lai J, Fields HL, Porreca F. Unmasking the tonic-aversive state in neuropathic pain. Nat Neurosci. 2009; 12:1364–6. [PubMed: 19783992]
22. Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, Echols S, Glick S, Ingrao J, Klassen-Ross T, Lacroix-Fralish ML, Matsumiya L, Sorge RE, Sotocinal SG, Tabaka JM, Wong D, van den Maagdenberg AM, Ferrari MD, Craig KD, Mogil JS. Coding of facial expressions of pain in the laboratory mouse. Nat Methods. 2010; 7:447–9. [PubMed: 20453868]
23. Freedman LP, Cockburn IM, Simcoe TS. The Economics of Reproducibility in Preclinical Research. PLoS Biol. 2015; 13:e1002165. [PubMed: 26057340]
24. Drummond GB, Paterson DJ, McGrath JC. ARRIVE: new guidelines for reporting animal research. J Physiol. 2010; 588:2517. [PubMed: 20634179]