

Frontiers of Analgesic Research

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In the last two decades, global research efforts directed at enhancing our collective understanding of the neurobiology of chronic pain have identified a considerable array of receptors, enzymes and ion channels as potential novel targets for the development of a new generation of analgesic drugs. However, translation of this wealth of basic science research data into new therapeutics for the management of pain in patients has proven challenging. Although many potential new pharmaceuticals in development fail due to toxicity/poor tolerability, poor pharmaceutical properties and/or unsuitable pharmacokinetics, lack of efficacy in analgesic clinical trials is also a factor contributing to the difficulties in research translation. As a result, there has been a recent critical re-examination of key elements of the new drug development process for novel analgesics and this is a current frontier of novel analgesics research¹⁻⁴. Areas for improvement include further refinement of animal pain models to improve their ability to successfully predict efficacy in clinical trials in humans¹⁻³ as well as improving the quality of the design, conduct and reporting of 'proof of concept' efficacy studies conducted using these models². When assessed against the criteria used to judge the quality of clinical studies undertaken in humans, the quality of many animal pain studies published in peer-reviewed journals is quite poor². Significant deficiencies include failure to comment on whether or not animals were randomized to particular treatment groups, whether or not observers involved in quantitative/semi-quantitative assessment of study endpoints were 'blinded' to treatment/dose, presence and severity of adverse effects, impact on animal general health status, and/or the number of animals entering the study that completed the study². To date, few studies undertaken using rodent pain models report pharmacokinetic (PK) data in addition to pharmacodynamic (PD) data². Incorporation of this dimension into preclinical efficacy study protocols in the pain field would enable PK/PD modeling to identify the target plasma concentration range for subsequent early phase human clinical trials. By addressing the aforementioned issues, the ability of animal efficacy studies to more effectively predict clinical trial outcomes (both positive and negative) of novel analgesic agents will be improved which should enhance successful translation of basic research findings into novel analgesic treatments, in the longer term.

References

1. Cortright et al. *Expert Opin Drug Discov* (2008) 3: 1099-1108.
2. Rice et al. *Pain* (2009) 139: 243-47.
3. Scholz and Yaksh (2010) *Anesthesiology* 112: 511-513.
4. Eisnach JC (2010) *Anesthesiology* 112: 509-510.