Human models of pain for the prediction of clinical analgesia

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Abstract

Human experimental pain models are widely used to study drug effects under controlled conditions. However, efforts to improve both animal and human experimental model selection, on the basis of increased understanding of the underlying pathophysiological pain mechanisms, have been disappointing, with poor translation of results to clinical analgesia. We have developed an alternative approach to the selection of suitable pain models that can correctly predict drug efficacy in particular clinical settings. This is based on the analysis of successful or unsuccessful empirical prediction of clinical analgesia using experimental pain models. We analyzed statistically the distribution of published mutual agreements or disagreements between drug efficacy in experimental and clinical pain settings. Significance limits were derived by random permutations of agreements. We found that a limited subset of pain models predicts a large number of clinically relevant pain settings, including efficacy against neuropathic pain for which novel analgesics are particularly needed. Thus, based on empirical evidence of agreement between drugs for their efficacy in experimental and clinical pain settings, it is possible to identify pain models that reliably predict clinical analgesic drug efficacy in cost-effective experimental settings.

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1. Introduction

Experimental human pain models (Box 1) have improved our understanding of the physiology and pathophysiology of clinical nociception, inflammation, and analgesia [6,17]. They represent sophisticated tools to assess the efficacy of analgesic drugs in humans. They also have the potential to limit the costs of analgesic drug development by predicting clinical success with fewer resources than are needed for large clinical trials. However, correct prediction of clinical analgesia in experimental studies crucially depends on the correct choice of the pain model for the relevant clinical pain target [38].

In biomedical pain research environments, the classical approach to model selection is based on the knowledge of pathophysiological mechanisms involved in both experimental and clinical pain settings. For example, the analgesic efficacy of the TRPV1 antagonist, AZD-1386, has been shown to be related to excitation of TRPV1 by painful heat [9,27]. Based on this mechanism, AZD-1386 should also be effective in osteoarthritic and postoperative pain, both shown to involve TRPV1 [3,33]. However, AZD-1386 failed in these clinical settings [12,51]. This failure could have been predicted by the negative data obtained with the experimental blunt pressure test [27]. But the mechanism-based selection approach provided no basis for disregarding heat in favor of pressure as a predictor of the analgesic efficacy of the TRPV1 antagonist.

Such failures indicate that mechanism-based model selection, although completely reasonable and in accordance with biomedical scientific principles, has its limitations. This has resulted in frequent disappointment and doubts about experimental pain models [36] and to a decrease in their use (Fig. 1). A reason for these failures is incomplete understanding of the mechanisms on which basis the model is chosen. This hampers mechanism-based model selection. Although more research on the underlying mechanisms will undoubtedly reduce this handicap, immediate enhancement of the predictive nature of pain models is needed to exploit their potential in drug development. Hence, we have developed an alternative means for choosing the relevant model, based on empirical evidence of agreement between analgesic drugs for their effects in experimental and clinical settings. Statistical methods were applied to identify the most predictive experimental pain models or combinations of models. We finally show that this approach

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would have predicted the recent clinical failure of TRPV1 antagonists. Prediction of clinical drug efficacy at an early stage of development is, therefore, already possible.

2. Methods

2.1. Data acquisition and compilation

A review in July 2012 of the available literature on analgesic efficacy in either clinical or experimental settings [38], which was updated on May 30, 2013, provided a data set of n = 22,644 items that was sufficiently detailed to allow generation of a set of predictive experimental pain models applicable to future drug development for various clinical pain settings. Evidence for analgesic drug efficacy in clinical settings was obtained by a Cochrane library search for “pain” and “analgesia,” which yielded 126 hits. This led to the identification of 37 clinical pain settings for which the analgesic efficacy of 18 different drug classes had been tested (for details, see Table 1 in the supplementary materials). Analgesic drug efficacy in clinical settings was assessed based on primary outcomes such as changes in pain intensity by at least 50%, ratings of pain intensity on visual analog or categorical scales, or third-party pain scoring. Secondary outcomes were opioid dosing requirements for breakthrough analgesia, the time elapsed until

<table>
<thead>
<tr>
<th>Subject</th>
<th>Assay (pain stimulus)</th>
<th>Measure (readout)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Etiology</td>
<td>• Psychophysics</td>
</tr>
<tr>
<td>Age</td>
<td>• Nociceptive</td>
<td>o Visual analog scales</td>
</tr>
<tr>
<td>Health status</td>
<td>• Electrical</td>
<td>o Numerical rating scales</td>
</tr>
<tr>
<td>Genetics</td>
<td>• Thermal (heat, cold)</td>
<td>o Questionnaires</td>
</tr>
<tr>
<td>Epigenetics</td>
<td>• Mechanical (blunt, punctate pressure)</td>
<td>o Pain threshold</td>
</tr>
<tr>
<td>Social factors</td>
<td>• Chemical (intranasal CO₂, nociceptive substances, capsaicin, menthol, hypertonic saline)</td>
<td>o Pain tolerance</td>
</tr>
<tr>
<td>Testing conditions</td>
<td>• Inflammatory</td>
<td>• Non-verbal</td>
</tr>
<tr>
<td>Body part</td>
<td>• Freeze lesion</td>
<td>o Behavior (mimics, vocalization)</td>
</tr>
<tr>
<td></td>
<td>• Intranasal dry air</td>
<td>o Autonomic parameters</td>
</tr>
<tr>
<td></td>
<td>• Reflex</td>
<td>(heart rate, skin temperature, electrical skin resistance)</td>
</tr>
<tr>
<td></td>
<td>• Single/Repetitive</td>
<td>o Microneurography</td>
</tr>
<tr>
<td></td>
<td>• Short/long lasting</td>
<td>o Reflex</td>
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<tr>
<td></td>
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<td>o PET</td>
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<td></td>
<td></td>
<td>o fMRI</td>
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<tr>
<td></td>
<td></td>
<td>o Cortical event-related potentials</td>
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<tr>
<td></td>
<td></td>
<td>o Peripheral nociceptive responses (NMP)</td>
</tr>
</tbody>
</table>

Experimental human pain models, like all models, provide a limited reflection of reality [50]. This reality is clinical pain, which is the most frequent reason for visits to a doctor and chronically affects one-fifth of adults in Europe, North America, and Australia (http://www.iasp-pain.org). Why, then, should analgesic efficacy be studied with models and not directly? In contrast to spontaneous clinical pain, experimental pain is controllable with regard to its spatial (localization), temporal (duration), quantitative (intensity), and qualitative (eg, “pricking” or “pressing” [5]) properties. Major confounders, such as analgesic therapy, can be avoided, and placebo-controlled cross-over designs can be applied to healthy subjects. Withholding analgesic therapy would be unethical in pain patients. However, models capture not all attributes of the original pain but only those considered as relevant [50], and these obviously vary in their ability to reflect clinical pain. This is the background to the present comparative analysis that made use of a further characteristic of models, which can itself be subject to modeling [50]: namely, the agreement between analgesic efficacy under experimental and clinical conditions.
administration of rescue analgesics, opioid-sparing effects of non-opioid drugs, patients’ preference, therapy withdrawals due to adverse events, or lack of efficacy. The 126 hits were classified into positive (+) or negative (−) evidence for analgesic efficacy, separately for drugs or drug classes. When the Cochrane Review stated that available evidence did not allow a final conclusion to be drawn, the study was rated as neither positive nor negative (±). Evidence for analgesic drug efficacy in experimental pain models was taken mainly from 2 comprehensive topical reviews [48,49] and supplemented by further PubMed search (for details, see Oertel and Lotsch [38]). This identified 34 different experimental pain models that had been used to assess analgesic drug effects.

2.2. Definition of drug efficacy agreement between experimental and clinical settings

A study was classified as reporting positive (+) evidence if drug-related analgesia was recorded in an experimental pain model by a statistically significant reduction in pain intensity, or increase in pain threshold or tolerance, or decrease in area of hyperalgesia or decrease in amplitudes of pain-related evoked potentials. Because available information on drug-induced analgesia in experimental pain models did not fulfill Cochrane criteria but was based on published results from single experiments, the evidence was rated as positive only when all experimental readouts of the specific test indicated analgesia. The same applied to negative (−) evidence. For example, if analgesia was assessed in an experimental test by concomitant measurement of pain intensity ratings and pain-related evoked potentials, both readouts had to indicate analgesia or no analgesia for the evidence to be rated as either positive or negative. When all readouts did not indicate analgesia or lack of analgesia, the study was rated as neither positive nor negative (±) with respect to the specific model. This coding strategy did not take into account the degree of analgesic efficacy or the magnitude of the drug effect.

2.3. Analysis of mutual agreement between experimental and clinical drug efficacies

The assumption driving this analysis was that if an analgesic drug was effective both in an experimental pain model and in a clinical pain setting, then the model might be predictive for the relevant clinical setting. Moreover, the validity of this prediction should increase with an increasing number of analgesic drug classes for which the agreement is shown. Therefore, the evidence for mutual agreements between analgesic efficacy in experimental and clinical settings was assessed as follows: When the review of the literature revealed that a drug was effective in both the respective clinical and experimental pain conditions, the positive relationship between clinical and experimental pain conditions was increased by 1. By contrast, in the case that the results disagreed between clinical and experimental efficacy, the negative relationship was increased by 1. The sum of the positive and negative relationships was called “common drug efficacy” (CDE). Thus, the CDE for a particular pain model was calculated as

\[
CDE_{\text{model}} = \sum \text{Agreement}_{\text{Clinic/Experimental}} - \sum \text{Disagreement}_{\text{Clinic/Experimental}}
\]

Evidence for mutual agreements between analgesic drugs for their efficacy in experimental and clinical settings was analyzed on the basis of the CDE values using Matlab software (MathWorks, Natick, MA). Specifically, the sum of CDE values for a specific experimental pain model was used to quantify the cumulative evidence for correct agreements with analgesic drug efficacy in clinical settings. This was called “total experimental agreement” (TEA; column sums in Fig. 2A).

2.4. Deriving statistical significance

To identify the numerical limits beyond which the above-identified TEA could be considered as significantly differing from

Fig. 1. Published reports of assessments of analgesic efficacy using experimental pain models according to a PubMed search for (pain model OR experimental pain OR noceboceptive stimul OR AND human) AND healthy; NOT review NOT “meta analysis”; NOT patient AND drug), where drug denotes a drug from 18 different drug classes that were subsequently included in the search (see table in the supplementary materials). The search was performed on May 30, 2013. The graph shows the total number of papers appearing in the PubMed database by year of publication, for all drugs and separately for selective cyclooxygenase (COX)-2 inhibitors, classic nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. The graph demonstrates that after an initial rise in total publication numbers until the end of the 1990s, this trend has come to an end, and lately the publication number per year seems to have declined. For COX-2 inhibitors, this reflects their abandonment in the late 2010s. However, the decline in total publications per year also indicates that experimental pain models seem to have been decreasing in popularity for analgesic drug assessments in the most recent decade.
chance, the TEA values were analyzed using a Monte-Carlo approach. That is, for 1000 random permutations of the columns (pain models, Fig. 3) and rows (clinical settings) in the matrix of CDE values, a distribution of random empirical agreement values (REA) was obtained. A Gaussian distribution was fitted to the REA distribution (Fig. 2B and C) using the Pareto Density Estimation method [52] as a suitable kernel density estimation procedure and the expectation maximization (EM) algorithm [12] for model optimization. This provided a cumulative distribution function (cdf0) and a cdf0(TEA(x)) value for the observed TEA values of a model x (Fig. 2D). In this way, P values were defined for the significance of TEA to lie outside the statistical confidence limits for better agreement than expected by chance, P(x) = 1 – cdf0(TEA(x)), or worse agreement than expected by chance, P(x) = cdf0(TEA(x)). The same approach was taken for the total clinical agreement (TCA), that is, the sum of the rows of the CDE values in the matrix of Fig. 3.

3. Results

In all, 22,644 items were obtained from published information on mutual agreements between analgesic drug efficacy. This included 18 different drug classes, 34 different experimental pain models, and 37 different clinical pain settings. On this empirical basis, predictive experimental pain models were identified.

The CDE values captured the total experimental agreement, TEA(x), for each experimental pain model x, between pain models and clinical pain settings (Fig. 3). Pain models could be grouped for TEA values into 5 groups according to the statistical significance at which the TEA value observed for a specific pain model deviated from the TEA value expected by chance, that is, (1) agreement better than chance at P < .05 or (2) P < .0001, (3) not significant, (4) worse than chance (disagreement between experimental and clinical efficacy) at P < .01 or (5) P < .05. The necessary TEA limits of statistical significance were obtained from analyzing a suitable model of random agreements using a Monte Carlo approach and deriving the confidence limits (p(x) and p(x) for agreement or disagreement) between empirical models and clinical pain beyond the probability limits expected by chance (Fig. 2). Limits of p(x) of 0.0001 and 0.05 and p(x) of 0.05 and 0.01 defined group (classes) of experimental pain models were defined from the convention, that is, 0.05, and from an analysis of the distribution of P values, which suggested a further meaningful limit at P < .001 (see supplementary Fig. S2).

The best values for TEA(x) were found in groups 1 and 2 (Fig. 3, green columns), which implies that TEA values ≥27 or ≥18 indicated correct predictions of clinical efficacy better by chance at P values smaller than .0001 and .05, respectively. The pain models included in these classes were thus supported by empirical evidence to provide correct predictions of analgesic drug efficacies in several different clinical settings (Fig. 3, green rows), significantly, at P < .0001 or P < .05, more often than expected by chance (Table 1). Specifically, a set of 4 pain models consisting of (1) chemical hyperalgesia combined with punctate pressure,
(2) UV-B induced hyperalgesia combined with contact heat, or (3) UV-B hyperalgesia combined with punctate pressure and (4) chemical pain induced via local application of short pulses of gaseous carbon dioxide onto the nasal mucosa, emerged from this analysis as models that were highly likely to provide predictions of analgesic drug efficacy that hold true in the most relevant clinical settings. By adding a further 5 models that provide better predictions than chance at $P < .05$, model advice was extended to, in total, a limited set of 9 pain models with $P < .05$ that could be regarded as clinically predictive with sufficient empirical support.
The present results were obtained from empirical evidence of agreement between analgesic drugs of their efficacy in human experimental and clinical settings. The data obtained may serve as an alternative basis for the selection of predictive pain models, that is, the statistical approach presented provides a possible short-cut for correct model selection compared to the pathomechanism-based approach in which the selection of predictive pain models is being based on known pathophysiology of experimental and clinical pain. This latter approach often provides unsatisfactory results, contributing to the belief that experimental human pain models have little utility for drug research and development. Nevertheless, as the present approach was based solely on currently available empirical evidence, the predictivity of pain models may change as empirical evidence continues to accumulate.

The results indicate that a small set of experimental pain models (Table 1) seems to be predictive for most drug development requirements. These models exhibited the highest significance for mutual agreements between experimental and clinical analgesic drug efficacy (classes 1 and 2, \( P < .0001 \) and \( P < .05 \), respectively). For these models, drug efficacy was consistently in agreement with pain settings in clinical pain classes 1 and 2, for which the efficacy of most classes of analgesics had been experimentally assessed. Specifically, a set of 9 human pain models seems to offer predictivity for experimental analgesic studies (Table 1). This set comprises a variety of nociceptive stimuli and readouts (Table 1) with a tendency toward combined models, such as UV-B hyperalgesia plus punctate pressure. Based on the highest CDE values with the highest statistical significance for lack of agreement with clinical settings due to chance (\( P < .0001 \), class 1 in Table 1 and Fig. 3), a minimum of 4 models offers a reasonable chance to predict the most frequently addressed clinical settings, that is, (1) chemical hyperalgesia plus punctate pressure or UV-B hyperalgesia plus punctate pressure, (2) blunt pressure, (3) chemical pain consisting of intranasal stimuli of gaseous \( CO_2 \) and (4) UV-B hyperalgesia plus contact heat. This set is small enough to be used within an experimental study to maximize its predictive value. Most of these models displayed almost perfect agreement with respect to analgesic drug effects, suggesting that they involve nociceptive or analgesic mechanisms that also play a role in the corresponding clinical settings. This may be particularly useful for the development of analgesics that are effective in neuropathic pain for which the need for novel analgesics is great [14]. For this purpose, intranasal gaseous \( CO_2 \) stimuli and electrical stimuli appear to be most predictive. In contrast, negative CDE values were often found for the popular laser heat pain model [8,11] as a predictive model for neuropathic analgesia. Nonetheless, the model seems to provide good predictions along with an overall high CDE, making it a highly recommended model in other settings. Ice water immersion and tourniquet models rarely provided results that agreed with clinical analgesia and are therefore not advised for drug studies.

By taking the present statistical approach, the failure of the TRPV1 antagonist, AZD-1386, in osteoarthritic [51] and postoperative [42] pain would have been predictable. Of note, neither of these studies was included in the present analysis, and therefore the application of the present approach can be regarded as demonstrating their prospective utility. Specifically, the application of the method that we describe indicates that contact heat (class 5 of the experimental models, Fig. 3) is not suitable to predict analgesic efficacy in osteoarthritic and postoperative pain (class 1 of the clinical pain settings). By contrast, blunt pressure (class 2 of the experimental models) seems to be suited to predict analgesia in postoperative pain and osteoarthritis. Indeed, blunt pressure generated negative evidence for the analgesic efficacy of AZD-1386 (pressure to the lateral site of the extensor digitor muscle [27]). Thus, the approach described here would have recognized the inefficacy of AZD-1386 in the blunt pressure model as a correct prediction of its failure as an analgesic in osteoarthritis and postoperative pain.

The present approach provides a probability structure for mutual agreements between analgesic efficacy in experimental and clinical settings based on available empirical evidence. In this approach, the pattern of analgesic drug efficacy in experimental pain could be allocated to the same class as that for efficacy in clinical pain settings. The method necessarily fails when empirical evidence is lacking. Therefore, the class allocation does not completely reflect pathophysiology. Assignment of central neuropathic pain to class 4 cannot be interpreted as an error of the method to recognize neuropathic pain; rather, the sparse information on analgesic drug efficacies in this setting determined a pattern of CDE values similar to those for other kinds of neuropathic pain for which more analgesic efficacy information is available from structured Cochrane Reviews.

<table>
<thead>
<tr>
<th>P of success</th>
<th>Experimental pain model</th>
<th>Stimulus</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P &lt; .0001 )</td>
<td>Chemical hyperalgesia + punctate pressure</td>
<td>Capsaicin + pinprick/von Frey hair</td>
<td>Psychophysics</td>
</tr>
<tr>
<td>( P &lt; .0001 )</td>
<td>UV-B hyperalgesia + contact heat</td>
<td>UV-B radiation + Medoc TSA-II thermode</td>
<td>Event-related potentials</td>
</tr>
<tr>
<td>( P &lt; .0001 )</td>
<td>UV-B hyperalgesia + punctate pressure</td>
<td>UV-B radiation + pinprick/von Frey hair</td>
<td>MEG</td>
</tr>
<tr>
<td>( P &lt; .0001 )</td>
<td>Chemical pain (nasal)</td>
<td>Intranasal gaseous ( CO_2 )-stimuli</td>
<td>IMRI</td>
</tr>
<tr>
<td>( P &lt; .05 )</td>
<td>Electrical hyperalgesia + punctate pressure</td>
<td>Pressure algometry</td>
<td>PET</td>
</tr>
<tr>
<td>( P &lt; .05 )</td>
<td>Electrical hyperalgesia + punctate pressure</td>
<td>Electrical sine wave current + pinprick/von Frey hair</td>
<td>FMRI</td>
</tr>
<tr>
<td>( P &lt; .05 )</td>
<td>Punctate heat</td>
<td>Laser heat stimulus</td>
<td>PET</td>
</tr>
<tr>
<td>( P &lt; .05 )</td>
<td>Chemical hyperalgesia</td>
<td>Hypertonic saline injected intramuscularly</td>
<td>PET</td>
</tr>
<tr>
<td>( P &lt; .05 )</td>
<td>Electrical pain</td>
<td>Electrical sine wave current</td>
<td>PET</td>
</tr>
</tbody>
</table>

For these models, drug efficacy was consistently in agreement with pain settings in clinical pain classes 1 and 2, for which the efficacy of most classes of analgesics had been experimentally assessed. Specifically, the present approach provides a probability structure for mutual agreements between analgesic efficacy in experimental and clinical settings based on available empirical evidence. In this approach, the pattern of analgesic drug efficacy in experimental pain could be allocated to the same class as that for efficacy in clinical pain settings. The method necessarily fails when empirical evidence is lacking. Therefore, the class allocation does not completely reflect pathophysiology. Assignment of central neuropathic pain to class 4 cannot be interpreted as an error of the method to recognize neuropathic pain; rather, the sparse information on analgesic drug efficacies in this setting determined a pattern of CDE values similar to those for other kinds of neuropathic pain for which more analgesic efficacy information is available from structured Cochrane Reviews.
The main outcome of our analysis was the identification of those experimental human pain models that currently have the highest likelihood to provide desirable results for drug development, that is, evidence of a drug’s analgesic efficacy that also holds true in clinical settings. Model selection for particular studies, nevertheless, remains a task that requires intimate knowledge of human pain. In particular, in settings in which empirical information is sparse, model selection must still depend on the classical mechanistic method. Thus, further development and validation of promising models that lack sufficient evidence to generate a high CDE score is warranted. For example, the cold-menthol human pain model predicted the analgesic actions of pregabalin, pinpointing this as a potential further valid model for neuropathic pain [1]. This role is biologically plausible, as cold allodynia is a symptom in patients with neuropathic pain that is often resistant to analgesic treatment [14]. As data on both methods are limited, in terms of sparse empirical evidence and incomplete pathophysiological knowledge, a combined assessment of both approaches appears advisable. In addition, by choosing a data-driven approach, not all physiologically related clinical settings necessarily fall into the same group, as some may have been analyzed less often than others. This simply emphasizes that the evidence-based model selection approach has its limitations. Thus, the classification of clinical models must be regarded as a separate form of classification for the pathophysiology of pain.

The results were notably robust, as similar results were obtained using an alternative approach consisting of a bi-cluster analysis [28,55]. Specifically, CDE data were submitted to a hierarchical clustering using the Ward algorithm [13] and applying the Euclidean distance between the row or column vectors of CDE values. This approach also identified 5 groups of experimental pain models that shared similar efficacy observations on drugs tested for analgesic effects, completely agreeing with the results of the main data analysis presented in this article. For comparison with the present results, the results of the alternative Ward cluster analysis are added as supplementary Fig. 53. The classification approach was finally preferred to bi-clustering methods [28,55], due to the small data space (34 × 37) resulting in a rough distribution of distances.

The present analysis did not distinguish between “no evidence” and “inconsistent evidence,” as “no evidence” was taken as 0. This could also result from the sum of 1 agreement (+1) and 1 disagreement (−1) between experimental and clinical analgesia. However, by focusing on models with the most extensive evidence for mutual agreements, neither no or inconsistent evidence would discourage recommendation of the best model. Models assigned a sum of 0 would not have qualified for recommendation, either when the 0 reflected lack of evidence or when 0 reflected inconsistent evidence. As shown in Fig. 3, only 5 models lacked any evidence, namely, balloon heat, dry air, glutamate injection, hot water immersion, and CO2 sensations induced by CO2. For comparison, only 2 models lacked evidence, namely, balloon heat and dry air.

The present statistical approach showed that one may successfully use findings obtained using experimental pain models to predict clinical analgesia. A confined set of experimental human pain models appears to be sufficient to correctly predict the analgesic drug efficacy for a set of clinical pain settings, including varieties of neuropathic pain, as a major goal of drug development. The method presented represents a positive alternative to the classical pathomechanism-based approach to pain model selection. As evidenced by its use, for instance, for drugs acting at TRPV1, model selection may have to be subject to modification when the evidence changes. This is not a specific property of the approach taken, because as knowledge of pathomechanism changes, so must the pathomechanism-based selection of models also change. By aligning both methods, experimental pain models can fulfill their potential to facilitate analgesic drug development as a cost-effective tool.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2014.07.003.

References


