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BRAIN RESEARCH REVIEWS

Review

Predicting therapeutic efficacy — Experimental pain in human subjects

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ABSTRACT

The pharmaceutical industry faces tough times. Despite tremendous advances in the science and technology of new lead identification and optimization, attrition rates for novel drug candidates making it into the clinic remain unacceptably high. A seamless boundary between basic preclinical and clinical arms of the discovery process, embodying the concept of 'translational research' is viewed by many as the way forward. The rational application of human experimental pain models in early clinical development is reviewed. Capsaicin, UV-irradiation and electrical stimulation methods have each been used to establish experimental hyperalgesia in Phase-I human volunteers and the application of these approaches is discussed in the context of several pharmacological examples. However, data generated from such studies must be integrated into a well-conceived and executed series of Phase-II efficacy trials in patients in order to derive maximal benefit. The challenges involved in optimal Phase-II/III trial design are reviewed with specific attention to the issues of sample size and placebo response. Finally, the application and potential of cortical EEG studies are discussed as an objective alternative to more conventional pain assessment tools with specific examples of how this technique has been applied to the study of NSAID and opiate-based therapeutics.

Contents

4. Proof of efficacy and dose-dependency of NSAID and opiate analgesics in Laser evoked potential paradigm — using capsaicin and UVB skin model (K. Schaffler, HPR)

Significant issues in the assessment of different clinical pain states arise mainly as a consequence of how patients' clinical impressions are measured. The quality and intensity parameters of an individual's sensory perception are normally only recorded in a subjective manner, usually via analogue or categorical scales or using pain diaries — but not in an objective/quantitative approach. These measures are often confounded by co-medications and by additional pathophysiological, cognitive- and vigilance-based influences. Therefore such instruments are not ideally suited to the detailed investigation of pain processing — tracing its peripheral and central pathways, and elucidating the respective underlying mechanisms.

The same holds for the evaluation of the general and specific efficacy of analgesic compounds. The human "black box" should allow additional enlightenment of diverse objectives, depicting efficacy principles (pharmacological targets), as well as time- and dose-efficacy of analgesic compounds. The application of laser technology as a novel, alternative or complimentary, technique in human pain research (laser algesimetry) has resulted in a major advance in our ability to generate and interpret noxious thermal sensations.

In pain measurements, the temperature at the skin surface has to be raised (>43 °C) in a very short time-frame to overcome the thresholds of the heat-sensitive pain receptors (thermo-nociceptors) and to open their heat-sensitive ionic channels (TRPV1) and to avoid adaptation (desensitization). This may be achieved, very effectively, using a constant-duration (fixed input length) nociceptive CO_2-laser beam - with the added advantages of this being a contact-free approach that offers individually-adjusted intensity settings all over the entire study period. The depth of penetration of the laser is low — resulting in a high receptor specificity because the stimulus exactly reaches the free nociceptive terminals (features dictated by the beam's wavelength in the far infrared spectrum with a maximum absorption in water). These precise stimuli can be repeatedly applied, without habituation, on normal and irritated/hyperalgesic skin — e.g. by introducing UV-irradiation or topical capsaicin exposure. Analgesic and anti-hyperalgesic properties of drugs can be demonstrated objectively and quantitatively by alterations of the somatosensory evoked potential (SEP) parameters, measured using Vertex-EEG sequences, mainly by reductions of signal amplitudes — e.g. vs. placebo.

Stimulus-response specificity is determined by triggering, filtering and averaging of several artefact- and contact-free painful stimuli. The first two main EP-components (**Fig. 1**) are evaluated with regard to their complex peak-to-peak (PtP) amplitude as well as with regard to the single N2-component, mainly reflecting 'peripheral' effects (Schaffler et al., 1992), and P2-component, mainly reflecting 'central' effects in pain relief mechanisms (Schaffler et al., 1991).

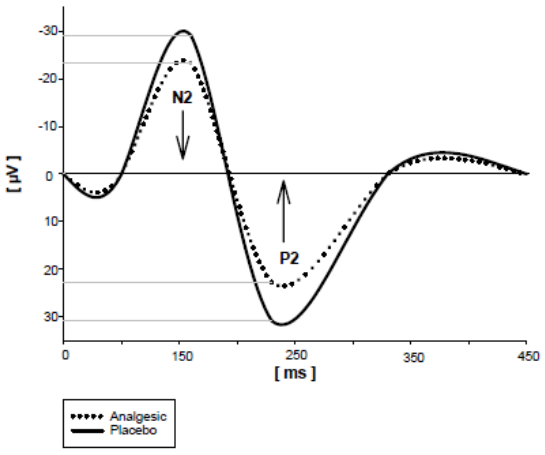


Fig. 1 – Principle components of the Laser SEP (N2- and P2-peaks) with a typical overlay of analgesic vs. placebo waveforms

Analgesics of the peripheral type are preferably expected to depress the N2-amplitudes and to a lesser extent the P2-amplitudes. Analgesics of the central type seem to depress preferentially the P2-amplitude and to a minor extent the N2-amplitude.

The laser-EPs can be used for different types of interpretations:

- Determination of sensory stimulus-intensity relationship (efficacy).
- Localizing type and pathways of pain-processing (peripheral and/or spinal/central preference).
- Quantification and comparison of the effects of different analgesics and analgesic combinations (general efficacy, onset, dose- and time-efficacy relationship).

Examples of the principal compound classes investigated, thus far, using the laser model include the following: NSAIDs (unspecific COX1–2 and COX2-selective inhibitors), opioids, opiates, anti-histamines, anti-depressants, anti-epileptics, topicals and others (for additional details see **Table 1**).

Table 1 – List of investigated typical and atypical analgesics by Laser-SEPs

NSAIDs
Celecoxib oral
Dexketoprofen trometamol oral
Diclofenac i.v.
Dipyrone i.v.
Etoricoxib oral
Ibuprofen (raceme and enantiomer)
Karprofen oral and i.v.
Ketorolac oral
Lysine clonixinate oral
Naproxen
Rofecoxib oral
Parecoxib i.v.
Valdecoxib oral
ASA and ASA-like
ASA oral
EBA (Ethoxy-benzoic acid) solution
Ethenzamide oral
Eugenol solution
Acetaminophen/Paracetamol
Narcotics
Cannabinoid agonists oral and i.v.
Codeine oral
Kappa agonist oral and i.v.
Morphine oral
Oxycodone oral
Pentazocine oral and i.v.
Remifentanil i.v.
H1-antagonists
Dimethindene oral
Orphenadrine i.v.
ReN1869 (amitriptyline-derived) oral
Diphenhydramine oral
Others
Capsaicin antagonist oral
Reboxetine (NARI) oral
Ethanol oral and i.v.
Flupirtine (pyridine derivative) oral
Granisedron (5-HT_3 agonist) [a]
Meprobamate oral [a]
Propofol i.v. [a]
Tapentadol oral
Tramadol oral and i.v.
Antiepileptics
CM40907 oral
Gabapentin oral
Topicals
Dimethindene gel 0.1% (antihistamine)
DMSO solution with and without additives
Lidocaine gel 2%
Lidocaine solution and lozenges (oral cavity)
ASA powder
B1-antagonist (blocks bradykinin) [a]
NK1-antagonist (blocks substance P) [a]
[a] Showing minor or no analgesic potency.

The laser-EP technique offers several advantages that are particularly relevant to the issue of increasing clinical trial efficiency, by decreasing overall risk:

- The laser approach enables us to work in small groups of healthy subjects (e.g. 18 to 24 people) – due to a low variability – and in an ethically acceptable intra-individual crossover approach, without additional impacts on suffering patients in clinical pain situations.
- The risks of local adaptation, or sensitization, are low in this highly-selective stimulation of heat-sensitive (nociceptive) ionic channels— due to random positioning of the noxious laser beam.
- Pharmacological effects of compounds can be evaluated on up to 3 different skin types simultaneously in each subject participating in the trial, and each person can contribute as his own control in homogeneous repeated measurement designs.

- There is excellent congruency of subjective with objective-quantitative measures. An example is shown in **Fig. 2**, in which the temporal aspects of both subjective (VAS) pain score and objective (LEP amplitude) measurements are compared in an acute UV-induced hyperalgesia paradigm for more than 24 h. This figure also illustrates the various options for analgesic treatment interventions: drug administration in a pre-emptive, in an acute, or in steady-state of pain/hyperalgesia conditions.

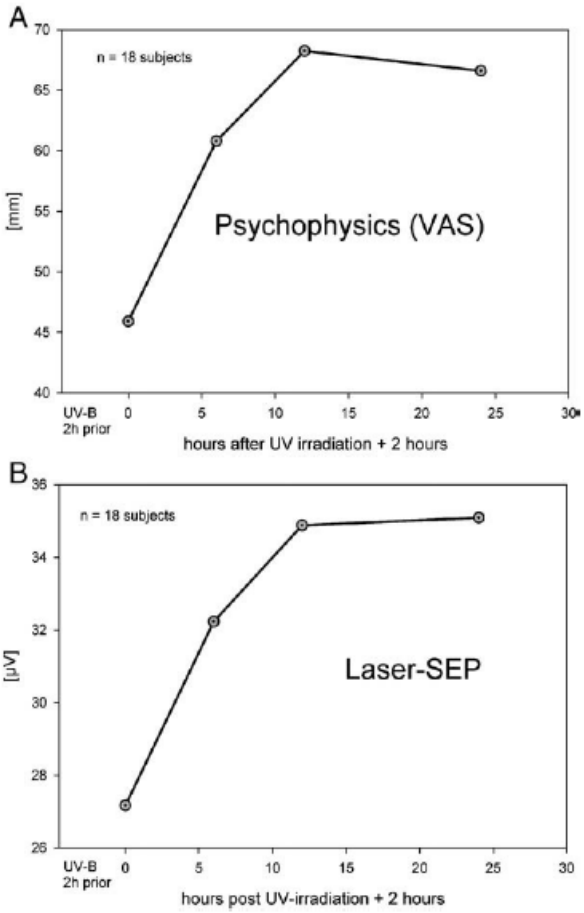


Fig. 2 – (A) Time course of VAS pain score in post UV-irradiation hyperalgesia development (congruent to LEP). **(B)** Time course of peak-to-peak (PtP) amplitude of Laser-EPs in post UV-irradiation hyperalgesia development (congruent to VAS).

- Ability to discriminate analgesic and anti-hyperalgesic actions. This is nicely illustrated by comparing laser-evoked pain (VAS scores) for acetaminophen/paracetamol (APAP) in normal and UV-sensitized skin conditions. On normal skin (**Fig. 3A**) there is no obvious hyperalgesia development after multiple Laser exposures over the course of a day and acetaminophen/paracetamol (APAP) does not present effective analgesia in this non-sensitized skin condition. After application of UV-B (**Fig. 3B**) there exists a distinct hyperalgesic development with successive laser exposures over the assessment day and a significant anti-hyperalgesic effect of acetaminophen/paracetamol is discriminated vs. placebo (despite lack of anti-inflammatory properties of APAP).
- Ability to discern additional mechanistic information from drug action. The comparison of normal and UV skin conditions in laser PtP amplitudes adds additional information on drug action. For example, when comparing a NSAID and an opioid (**Fig. 4A and B**), the NSAID was – as to be expected – not effective in the normal (non-inflamed) skin paradigm, but opioid efficacy was evident. Furthermore, the stability of the responses to laser stimulation over the course of a day is nicely demonstrated in the normal skin/placebo condition (plateau), confirming the lack of habituation/tolerance development over the day. In contrast, both drugs were effective in the UV-sensitized/hyperalgesic skin condition, showing that the NSAIDs principal therapeutic domain are inflammatory states, but (as expected) the opioid was also effective in raising basic nociceptive thresholds (attenuating LEP PtP-amplitudes).

The application of LEP to mainstream experimental pain studies is relatively new, but the technique is gaining interest and momentum. Benchmarking LEP against more traditional 'instruments' will be crucial to the further development and application of this procedure — and some progress has been made in this regard.

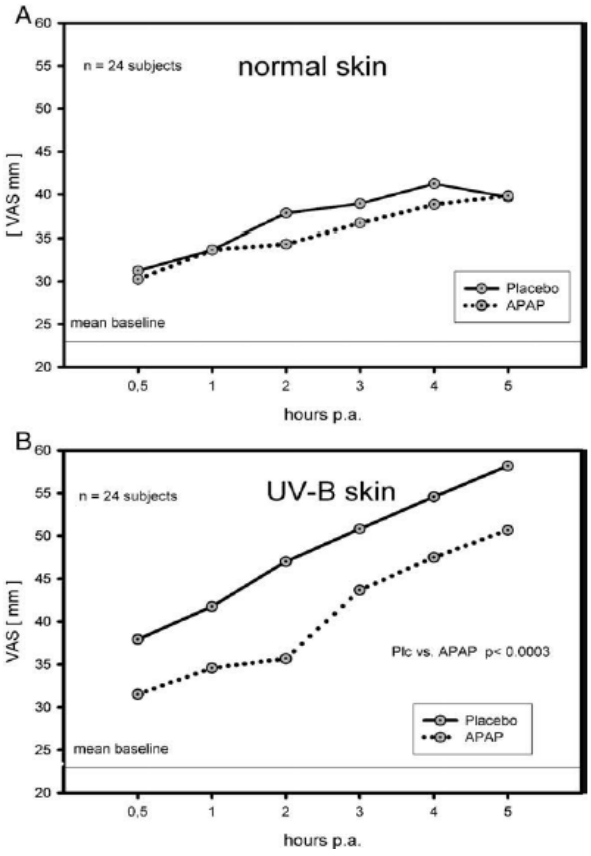
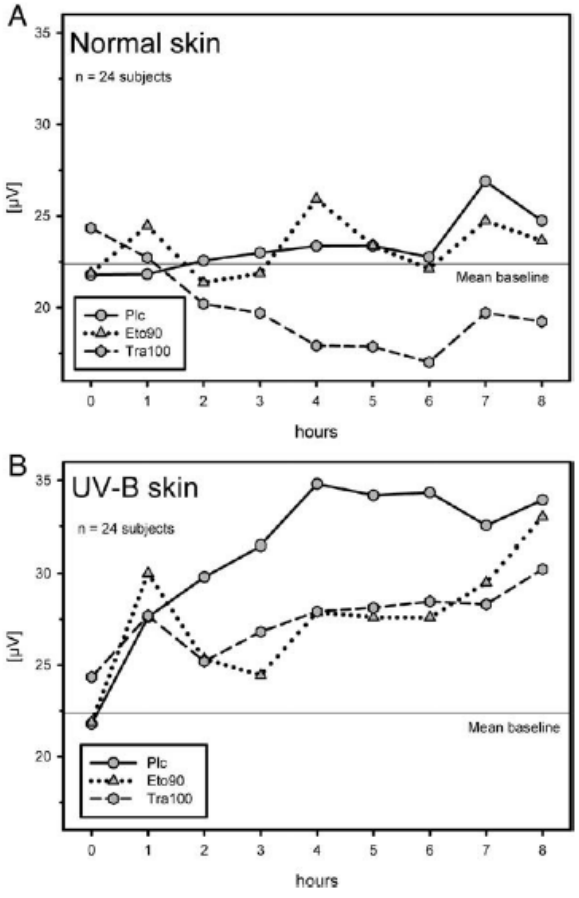


Fig. 3 – (A) Laser-SEPs in normal skin conditions showing low hyperalgesia development over time and the lack of discrimination between drug (APAP) and placebo. **(B)** Laser-SEPs in UV-B irradiated skin conditions showing developing hyperalgesia and distinctly better discrimination of drug (APAP) effect vs. placebo.

Fig. 4 – (A) Laser-SEPs in normal (non-inflamed) skin conditions. Note the stable placebo LSEP signal and the lack of habituation to thermo-nociceptive laser stimulation. Opioids show robust efficacy whereas NSAIDs are ineffective on normal skin nociceptive thresholds. **(B)** Laser-SEPs in UVB (inflamed) skin conditions. Note the time-dependent increase in placebo signals during thermo-nociceptive laser stimulation (indicating the development of hyperalgesia) and the good efficacy seen with both oral NSAID and oral opioid.



For example, a meta-analytical approach comparing peak-to-peak amplitude mean values of several established analgesics in studies using laser stimuli on capsaicin-sensitized skin were re-evaluated (regression) with respect to their dependency on laser amplitude and VAS pain score reduction (**Fig. 5A**). All drugs in the sample set clustered above a (N2–P2) peak-to-peak amplitude reduction of 2.5 μV or more (and a VAS score reduction of more than 10%). Statistically significant peak-to-peak amplitude differences were already reached with about half of these changes in LEP amplitudes. The declared 'starting level' of clinical relevance for the respective parameters in this test paradigm was set at two-fold the statistically significance level (about 2.5 μV) and the data revealed that clinical experience fits quite well with the ranking/clustering of the drugs (**Fig. 5A**). Furthermore, **Fig. 5B** shows that the 3 groups/clusters are adequately treating the respective stages of pain (mild–moderate–severe) — e.g. Tramadol 50 mg–Tramadol 100 mg–Remifentanil (Schaffler, 2006).

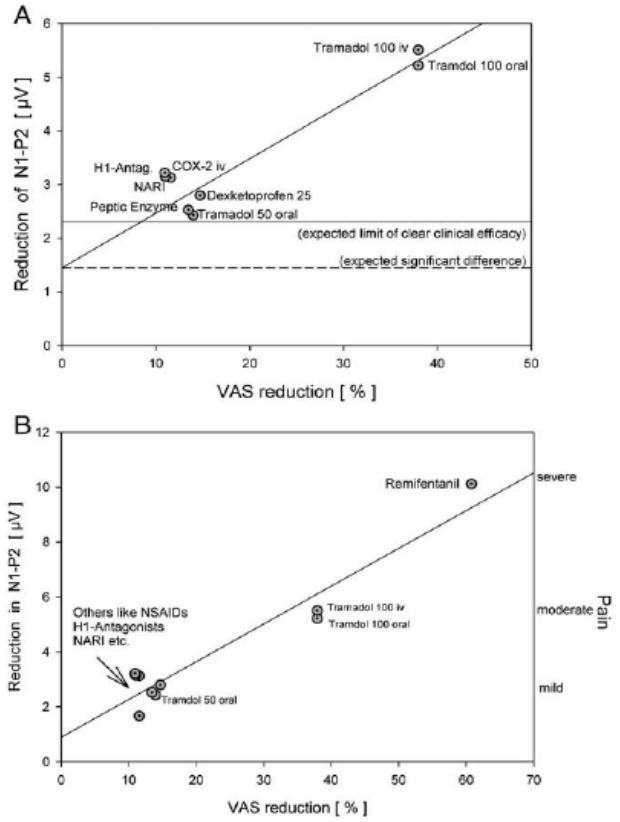


Fig. 5 – (**A**) Regression of LSEP amplitude vs. VAS pain score reduction in capsaicin-sensitized skin (p.a. means). A meta-analysis of available data was performed to cluster diverse analgesics with known clinical efficacy to define the threshold of clinical efficacy. The threshold is about twice the limit of significant detectable reductions in LSEP amplitude, illustrating the sensitivity of the LSEP technique. (**B**) Same regression, but extended to a highly potent opiate (remifentanil) demonstrating that the analgesic "clusters" show good alignment with treatment definitions of mild, moderate and severe pain states.

Thus laser-EPs represent a path to proof of concept by facilitating go/no-go decisions and distinctly reducing preparation time and the expenses of the subsequent, and more extensive, patient studies required for registration. The following pharmacological effects can be investigated in an ethically acceptable mode in healthy humans with an experimental (objective-quantitative, high-resolution) algesimetric approach — using a standardized and reproducible (radiant-heat/thermo-nociceptive) pain induction with Laser-EPs in different skin conditions (normal, UVB, capsaicin):

- Efficacy and mechanisms in general
- Dose- and time-efficacy, onset of efficacy
- Mode of drug administration regimen (e.g. single and multiple dose administrations or pre-emptive administration, acute, and (sub-) chronic interventions)
- Drug combination evaluations

The laser paradigm can also be considered as a tool of choice for a translational approach (animal–healthy subject–patient). Additional support for the laser model was recently bestowed by the "European Federation of Neurological Societies" (EFNS citation from the Laser Workshop at the NeuPSIG congress June 2007 in Berlin, see also Cruccu et al., 2004) – which indicated and recommended the usefulness of LSEP application in diagnostics of neuropathy – especially to distinguish between large and small fiber neuropathy.

There are certain issues with the laser approach that warrant consideration. For example, application of the procedure to chemically-sensitized skin may be compromised in cases where the topical agent has a high water content (e.g. unguents and gels), because of the high absorption of the CO_2-laser's infrared energy in water. However, this is usually a minor problem that may be overcome by washing and drying the skin prior to the stimulation procedure and if a more "permanent" sensitization is desired, the topical agent may be re-applied after the test session. The most significant limitation of the laser approach is that is cannot test the "mechanical" aspects of pain (i.e. the mechano-sensory modality changes in an area of secondary hyperalgesia, e.g. around a capsaicin application area for example). However, laser stimulation may be augmented by separate mechanical stimuli and both may be quantified using vertex SEPs, permitting both MEP and LEP readouts.

5. Concluding remarks

A general consensus throughout the pharmaceutical industry favors implementation of a range of measures to reduce the high levels of attrition currently associated with drug development. This will likely involve rethinking both preclinical and clinical paradigms and a closer alignment of these to implement a more efficient translational approach. The ideas discussed above represent only some of the thoughts and approaches currently being developed. An important component, not discussed, will undoubtedly come from the many molecular and tissue imaging strategies currently being applied to pain research and several promising studies/approaches have been describe recently (Ianetti et al., 2005; Borsook et al., 2007; Baliki et al., 2007). The pharmaceutical industry clearly has a number of options for PoA and PoC, and though there are hurdles ahead, the successful implementation of a revised approach to drug development will be driven by a combination of incentives that will include fiscal responsibility and scientific innovation.

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