



# Human Experimental Pain Models at Lifetree Clinical Research<sup>®</sup>

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### **Introduction**

Lifetree Clinical Research® (LCR) staff have long been pioneers in the development of robust human pain models to assess the efficacy of new analgesic drugs. Alice Jackson, R.N., co-founder and CEO of LCR, participated in the development of the highly successful and now validated bunionectomy acute pain model in 2000. Since that time, LCR has successfully utilized the bunionectomy model in multiple phase II-III clinical trials. Most recently, LCR's expertise was sought out to test the sensitivity of the bunionectomy model for non-opioid classes of compounds known to have analgesic efficacy. This ground breaking research was designed and executed in 2007, the results of which are targeted for publication in 2009.

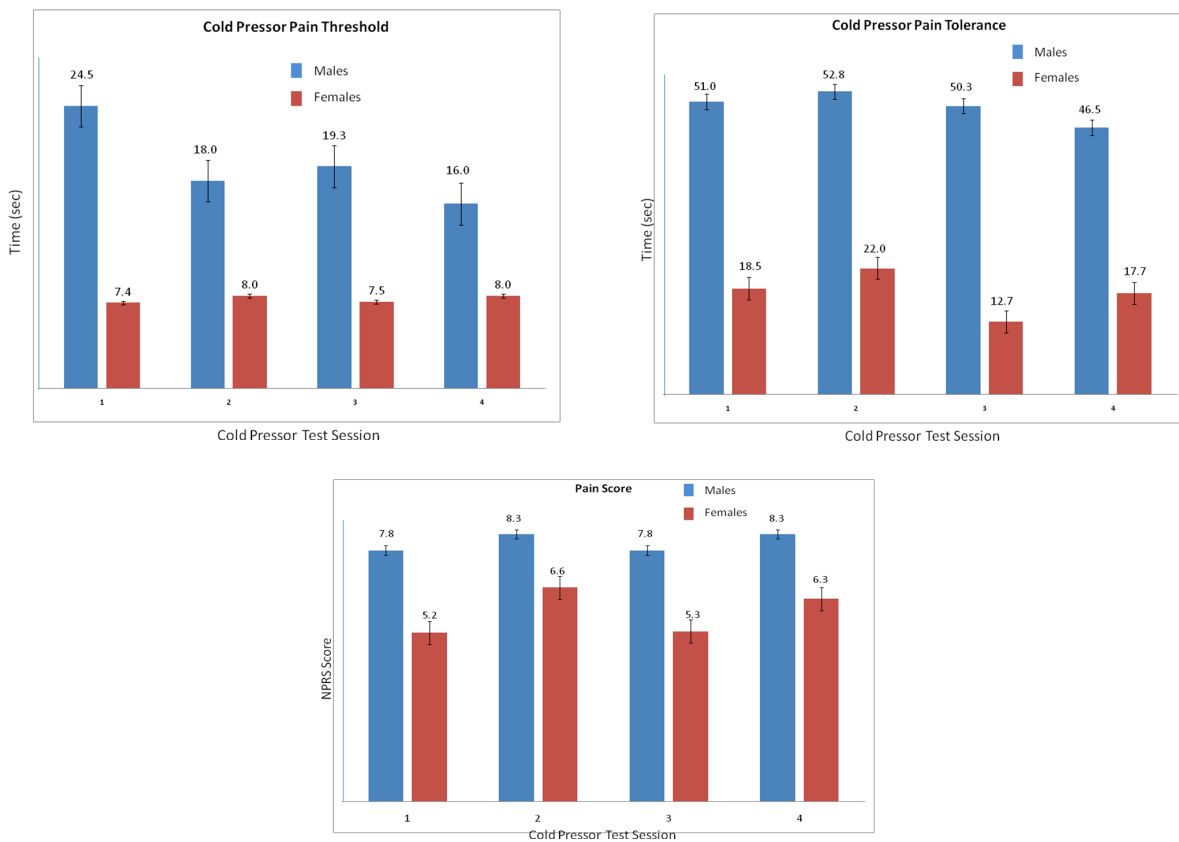
The wisdom tooth extraction model has also been used for many years to assess efficacy of acute pain analgesics. LCR has enrolled over 400 research subjects in this validated model, evaluating the analgesic efficacy of multiple investigational compounds across several pharmacological classes involving pioneering mechanisms of action.

In today's environment of continual strategic portfolio assessments, pharmaceutical and biotechnology companies are looking for early indications of efficacy during human safety testing and even making Go/No Go decisions at these development time points. In response to this need, LCR is pleased to offer our clients models of experimental pain with which analgesic activity can be demonstrated in Phase I trials in healthy volunteers. Specifically, the cold pressor, Neurometer®/QST, and heat/capsaicin models are described in greater detail on the following pages.

## COLD PRESSOR MODEL OF ACUTE PAIN

The cold pressor model is very sensitive to the analgesic activity of opioids (Jones et al., 1988; Escher et al., 2007). In this model, healthy volunteers submerge their non-dominant hand in ice cold (2-3°C) water. Endpoints include time to first perception of pain (pain threshold), time to withdrawal of hand (pain tolerance), and a subjective pain score (11-point NPRS) recorded at the time of withdrawal of the hand.

Our experience with this model is that these endpoints are robust and consistent over time for given research subjects based on baseline assessments (Figure 1), facilitating the demonstration of efficacy of new opioid drug candidates or formulations. We have replicated literature findings of differences in pain threshold and tolerance between males and females (Figure 1) (Mitchell et al., 2004).



**Figure 1.** Consistency of pain threshold, pain tolerance, and pain score over time in the cold pressor test in healthy male and female volunteers.



## **NEUROMETER<sup>®</sup>/QST MODEL OF PAIN**

A Neurometer<sup>®</sup> device is used as a method of quantitative sensory testing (QST) to selectively stimulate A $\beta$ , A $\delta$ , or c fibers using electrical stimulation. By varying the stimulus intensity, one can reliably determine pain threshold and tolerance using this technique. Such studies can be carried out in healthy volunteers and used to determine analgesic efficacy of investigational products (Gustorff et al., 2003). Deficits in pain perception in chronic conditions such as postherpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN) can be measured with Neurometer<sup>®</sup>/QST (Sakai et al., 2006; Winkler et al., 1999).

## **HEAT/CAPSAICIN MODEL OF NEUROPATHIC PAIN**

Moderate heat in combination with capsaicin in healthy volunteers has been shown to elicit hyperalgesia and allodynia resembling that found in chronic neuropathic pain conditions such as PHN (Dirks et al., 2002). With appropriate methodology, this response is stable over the course of several hours, allowing for the testing of investigational products. Using a pretreatment paradigm, one can evaluate the ability of a compound to prevent the development of hyperalgesia and allodynia. Alternatively, one can determine the ability of a drug to reverse established hyperalgesia and allodynia. Hyperalgesia and allodynia are routinely measured by responses to pin prick and light touch, respectively. The Neurometer<sup>®</sup> can also be used to test for drug efficacy using QST.



## REFERENCES

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