



Human Pain Models in Early Phase Drug Discovery

Human laboratory pain models refer to a set of methods usually conducted with normal healthy volunteers during which various stimuli are applied with the goal to activate nociceptive (pain) system and in this way it is possible to study pain physiology and effects of interventions, including to drugs and non-drug treatments.

A number of stimuli had been used for more than a few decades utilizing a wide range of stimuli and with the goal to activate specific pain mechanisms. For example, heat pain and ultraviolet burn activate small C-fiber system preferentially; electrical stimulation at lower intensity stimulates large fiber system while cold pressor activates peripheral A-delta fibers and centrally descending inhibition. As such, human laboratory models are used with administration of an intervention or a drug, and in that case they would be used to study specific mechanisms of action of that intervention or a drug.

Following are the human models, their descriptions and their principal features:

Heat pulse Test – are administered by means of contact or radiation (including laser), as single repeated stimulus (usually lasting only a few seconds) or as a series of stimuli. These are simple and could be used repeatedly. This is one of the most common methods in study of pain system. In addition to study of the mechanisms of pain transmission heat stimulation has been used for other mechanisms of pain processes and perception and in analgesic drug and non-drug studies.

Burn Test- is administered by means of contact heated probe or radiation (such as UVB) and it produces longer lasting experience of pain (hours) which has been utilized in analgesic drug studies.

Cold Pressor Test – consists of immersion of the limb into a container of temperature-controlled cold water. In addition to strong sensory component of cold pain, it also produces strong affective (usually negative) responses. There are 2 components to this test: pain intensity rating and pain tolerance. Pain intensity is reflective of pain transmission and perception while tolerance is a function of central pain modulation. This method demonstrated ability to discriminate effects of drugs from different classes. Consequently, it has been suitable for analgesic drug and non-drug studies.

Capsaicin Test – consists of application of capsaicin topically, intradermally and intramuscularly or to other tissues by other routes. There are 2 components to this test: initial pain (usually lasting minutes) due to activation of C-fibers with lingering pain (up to 30-45 minutes) in the range of mild to moderate, which also activates associated central pathways. That is followed by steady pain and manifestations of central sensitization (allodynia and hyperalgesia; usually lasting up to 30-60 minutes). Both components have sensitivity to analgesic drug and non-drug treatments.

Capsaicin-Heat Test – is a variation of capsaicin test and duration of pain, allodynia and hyperalgesia and are prolonged (two hours) by either contact or radiant heat.

Electrical stimulation Test– is administered via surface electrodes or via intradermal needles. This method also has 2 components: one due to activation of full range of fibers and affective component. This is the least used model.

Though straight forward in conducting these models, as reported in literature, one has to be aware of subject to subject variability and the inter- and intra-examiner variability that are always part of acute and chronic pain clinical trials. The degree of variability is markedly decreased with adherence to the study protocols and with adequate training and demonstrated proficiency of the clinical research staff. Here at the Lifetree Clinical Research we have made the necessary steps to train our clinical staff. Lifetree’s clinical research staff has the training and the demonstrated skills and expertise to minimize the intra-subject and inter- and intra-examiner variability with the goal of maximizing the likelihood of detecting the pharmacological signal that the drug or intervention under investigation would have.

Should you wish to discuss these models with one of our physicians and determine how best to incorporate the right model for your particular molecule please contact Lifetree Clinical Research® to set up a meeting.