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Sample Abstract

The Dolognawmeter: An Instrument To Quantify Pain Induced Oral Dysfunction

Investigating and curing human orofacial pain requires an animal assay that objectively measures impairment secondary to pain during oral function (gnawing) that is analogous to behavior that elicits pain in human patients (chewing). The dolognawmeter quantifies gnawing function in rodents. Composed of a confinement tube and spring loaded polymer dowels that actuate timers, the dolognawmeter precisely records the time required for a rodent to complete a discrete gnawing task. This instrument will facilitate evaluation of molecular mechanisms and analgesic therapies in an animal to set the stage for human clinical trials.

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Sample Student Essay

Problem: Chronic oral and facial pain from head and neck cancer, dental disease, jaw joint dysfunction and neurological disorders, is a major public health concern because of its incidence, intensity and refractory nature. To address this concern the United States Department of Health and Human Services through the National Institute of Health (NIH) released a Request for Applications (RFA) in 2006 to encourage research on orofacial pain by neurobiologists, pain experts and clinician scientists. The NIH sought to support “truly novel approaches that will lead to a better understanding of the pathophysiological mechanisms of chronic human pain disorders and the biological mechanisms of analgesic therapies” for head and neck pain. While the U.S. government has allocated significant resources to address the problem of orofacial pain among Americans, the impact and scope of orofacial pain is global. For example in India, the second most populous country in the world, *oral cancer* is the *most common cancer*. For oral cancer patients, pain is the primary determinant of a poor quality of life. In their final days, excruciating pain is suffered by 85% of those with this disease. Opiates (e.g. morphine) are only temporarily effective against orofacial pain and efficacy diminishes rapidly as opiate tolerance develops.

Understanding and treating orofacial pain has been extremely difficult because it was not possible to measure chronic orofacial pain in an animal model. Current measures of pain in animal models do not accurately reflect human chronic pain disorders because the available assays do not measure pain during normal, voluntary function of the animal. As a result, theories regarding the molecular mechanisms and targeted therapies for orofacial pain have been impossible to test. One common method used to evaluate oral pain in rodents entails visual monitoring of the animals after induction of pathology. Flinching of the head of the rodent is tallied and used as a proxy for pain. Such a method is not applicable to chronic pain. Moreover, such observational methods are time consuming, not objective, difficult to reproduce, and do not accurately reflect orofacial dysfunction - the primary and most obvious consequence of orofacial pain in both humans and animals.

Solution: I responded to the call from the NIH with an objective, noninvasive assay of chronic orofacial pain in an animal. I hypothesized that reduced gnawing function secondary to pain can be quantified in an animal model and used as an index of orofacial pain. The device that I invented, engineered, hand built and pilot tested quantifies progressive potentiation or attenuation of oral function to index degrees of pain over weeks or months. The apparatus (Figure1) is termed a dolognawmeter (dolor for pain; gnawmeter for the measurement of gnawing). Dr. Brian Schmidt and I co-wrote an NIH R21 grant application employing my invention and we received a priority score of 146, the best score of all 41 applications received from around the country for this RFA. The research will be funded and will be directed by Dr. Schmidt.

The dolognawmeter exploits the instinctual response of a mouse to gnaw an obstruction blocking forward movement in a confined tube. This instinct was noted by Ayada et al. (2002) in their work documenting gnawing activity in mice. Employing the instinctual gnawing response of a rodent in a tube is the only aspect of the apparatus that is not proprietary and original to the dolognawmeter. Exploiting this response ensures that the animal produces voluntary oral function during a gnawing task. The dolognawmeter automatically records the *amount of time* required to gnaw through multiple obstructions in a tube and consists of:

- 10”x 6”x 6” acrylic framework
- confinement tube (ID=25 mm) with a removable, perforated end cap
- two polymer dowels (OD = 8mm) that block the confinement tube in series at 2 cm intervals
- spring loaded pistons attached to the dowel that release the animal from the confinement tube once the dowels are severed
- timers actuated by pistons

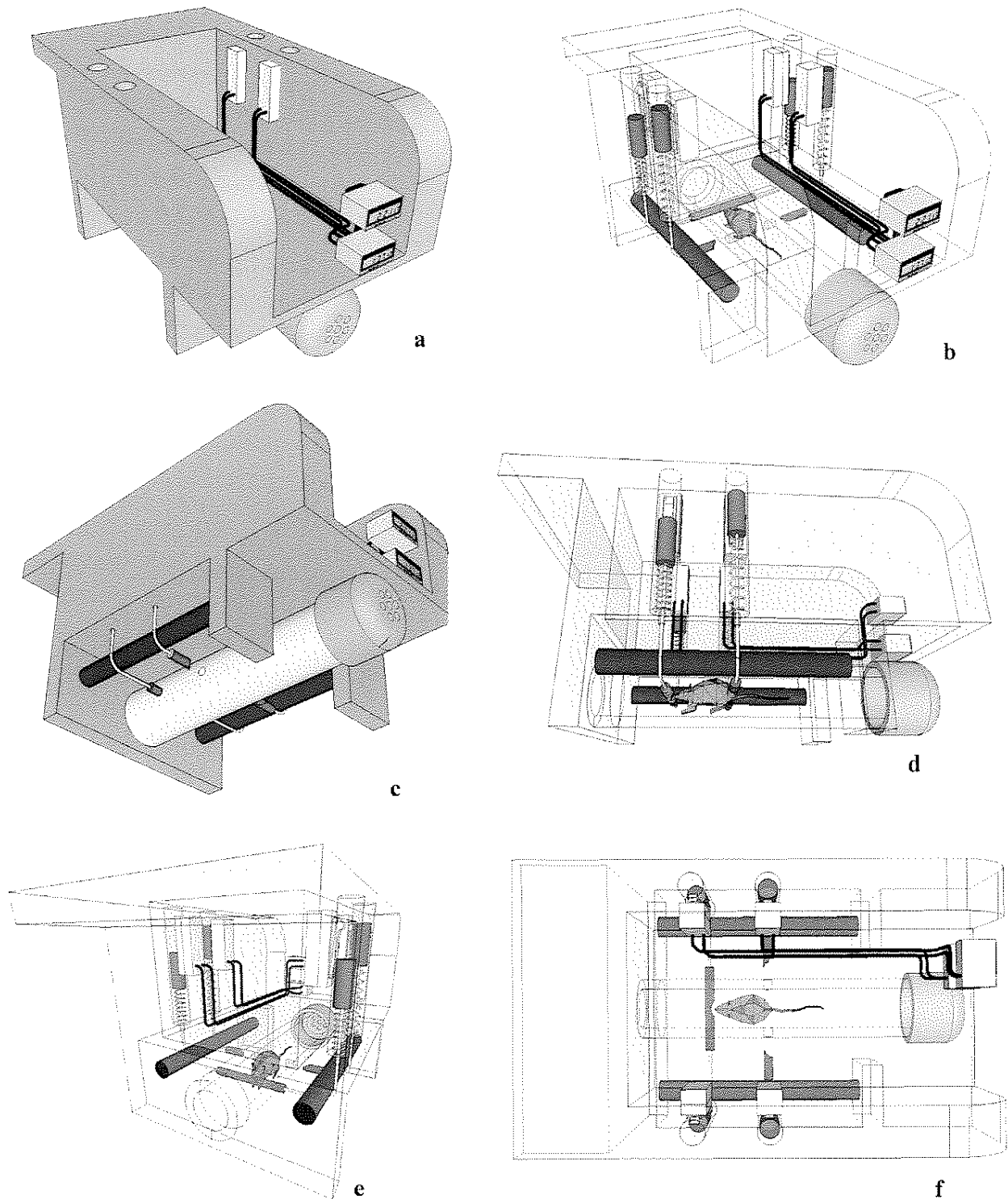


Figure 1. Three Dimensional Schematic of the Dolognawmeter. (a) Opaque quarter rearview. Removal of the perforated green cap allows loading of the animal into the device. (b) Transparent depiction in quarter rearview showing the animal gnawing the second dowel after severing the first dowel. The dowels are spring loaded and retract once they are severed. The second timer starts once the first dowel is severed. (c) Opaque bottom view of confinement tube. (d) Transparent side view with mouse in confinement tube. The first dowel has been severed and the mouse has begun gnawing the second dowel. (e) Transparent quarter frontview. Once the animal gnaws through the second dowel the animal is able to escape from the confinement tube and has access to the standard cage housing the dolognawmeter. (f) Transparent view from above.

The dolognawmeter fits into a standard clean-facility cage so that behavioral experiments occur within the regular cage, minimizing stress on the animal and decreasing the risk of disease transmission. Immunocompromised mice are required for experiments that involve inoculation of human cancer cells into experimental animals. Behavioral assays take place within the confines of an ultraclean facility that maintains the animal under filtered air in near sterile conditions. To reduce risk of disease transmission and to facilitate disinfection, the device isolates the mouse from the timers and dowel retraction mechanisms. During a gnawing session the mouse contacts only the internal surfaces of a removable and replaceable confinement tube, the end cap and the dowels. Once the mouse has made its escape from the confinement tube, it gains access to a truncated section of its regular cage where the acrylic face of the dolognawmeter creates one of the walls. All surfaces in contact with the animal can be rapidly cleaned and disinfected. Due to the configuration of the active cage ventilation system and the design of the dolognawmeter, fresh air is forced through the confinement tube and exits behind the mouse for the duration of the experiment. This configuration prevents overheating of the mouse in the small, thermally insulating confines of the tube.

Once a mouse is loaded into the confinement tube, a ventilated cap is placed on the back of the tube and the timer dedicated to the first dowel is manually started. Forward motion by the mouse is restricted by two polymer dowels in series. The dowels are attached to the body of the dolognawmeter with springs and are under tension at right angles to the long axis of the tube. Tension on the dowel is made possible by a mechanism in the dolognawmeter that independently spring-loads both ends of each dowel. When the animal severs the first dowel, the first clock is automatically stopped and both ends of the dowel spring away from the tube to allow forward movement of the mouse to a second dowel. Once the first dowel is severed, an actuator starts the timer dedicated to the second dowel. After the second dowel is severed the second timer automatically stops, the mouse escapes from the apparatus and is free to eat and drink within its truncated cage.

In our preliminary studies, healthy trained mice required approximately 25 minutes to gnaw through a dowel and demonstrate consistent gnawing behavior over more than 15 separate trials after training (Figure 2). Experimental comparisons are established as a percent change from an animal's own baseline value. We subsequently quantified pain behavior indexed by attenuation of gnawing in a human cancer model as well as an inflammatory pain model (Figure 3 and 4). Dr. Brian Schmidt directs the studies validating the dolognawmeter.

Since mice are nocturnal, all gnawing sessions take place in darkness. However, lighting must be employed during all pharmacologic injections of the mice and during placement of the mice into the apparatus. By comparing only the gnaw times for the second bar, all of the compared gnaw times are taken entirely in dark conditions, after habituation in the tube and isolated from human intervention. Moreover, the design of the dolognawmeter accommodates pharmacokinetic differences between animals and pre-empts difficulties with pharmacologic sedation, titration and drug onset. If pharmacologic agents are administered, an animal might delay gnawing on the

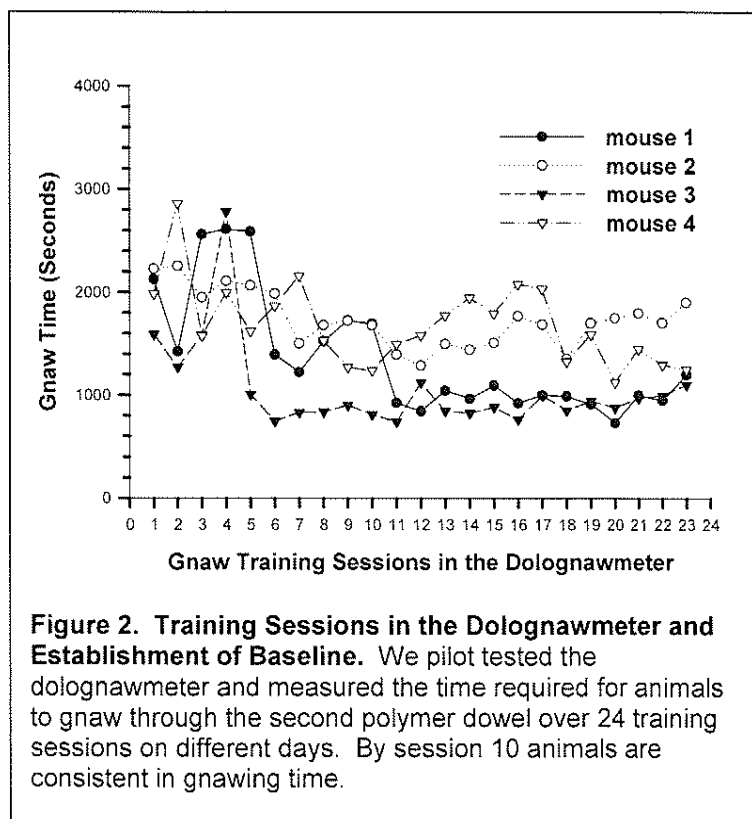


Figure 2. Training Sessions in the Dolognawmeter and Establishment of Baseline. We pilot tested the dolognawmeter and measured the time required for animals to gnaw through the second polymer dowel over 24 training sessions on different days. By session 10 animals are consistent in gnawing time.

first dowel until pharmacologic sedation has worn off or after analgesics have taken effect. The recorded gnawing time for the second dowel occurs only after the animal has completed an initial gnawing task and a minimum of confounders are present. For example, morphine reversal of pain is the gold standard against which novel analgesics are tested. However, morphine, like all opiates, has a sedative effect and an excitatory phase after induction. Accordingly, oral function can be drastically affected during its onset. The dolognawmeter pre-empts these confounders by allowing the animal to “start its own clock” for the second dowel. Once it severs the first dowel it has demonstrated progression beyond the most significant behavioral side effects of morphine.

Measurement of morphine-induced analgesia in a rodent model of orofacial pain is complicated by the induction of gnawing unrelated to pain relief- a side effect of morphine. This effect is termed gnawing stereotypy. Morphine induced gnawing stereotypy occurs while mice are in an upright position or while climbing. The dolognawmeter was specifically designed to preclude an upright position or climbing activity so that potentiation of gnawing solely reflects pain attenuation. Since the dolognawmeter blocks gnawing stereotypy, the analgesic effect of morphine is isolated in an orofacial pain model.

The dolognawmeter will for the first time allow laboratories to measure and compare chronic orofacial pain before and after experimental interventions. Besides producing critical data that simply have not been available until now, the device is very easy to use, is not technique sensitive, and requires only minimal training for personnel employing the device. The dolognawmeter is readily manufacturable and will be patented at the University of California San Francisco.

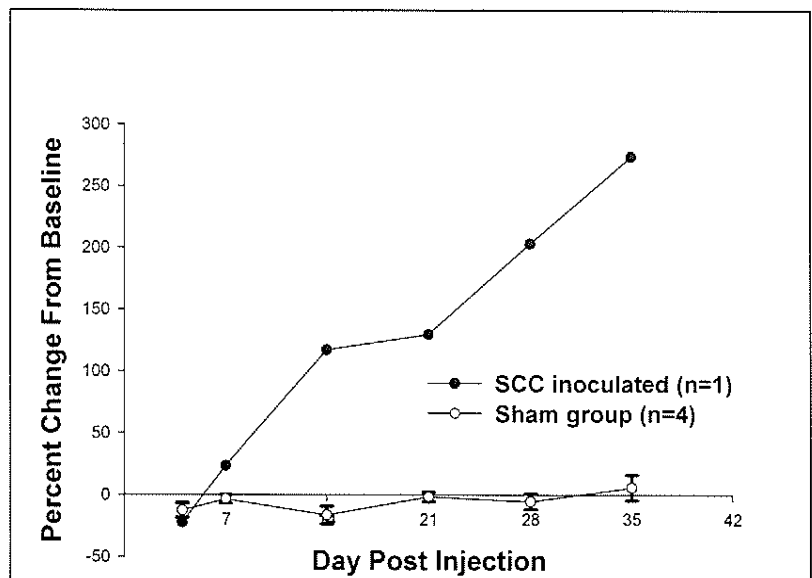


Figure 3. Change in Gnawing Function in the Head and Neck Cancer Model and Sham Group. The presence of the head and neck carcinoma lead to a progressive increase in the time required to gnaw through the polymer dowel as measured by the dolognawmeter. There was no increase in the gnawing time for the sham group that received an inoculation of only the cell culture media.

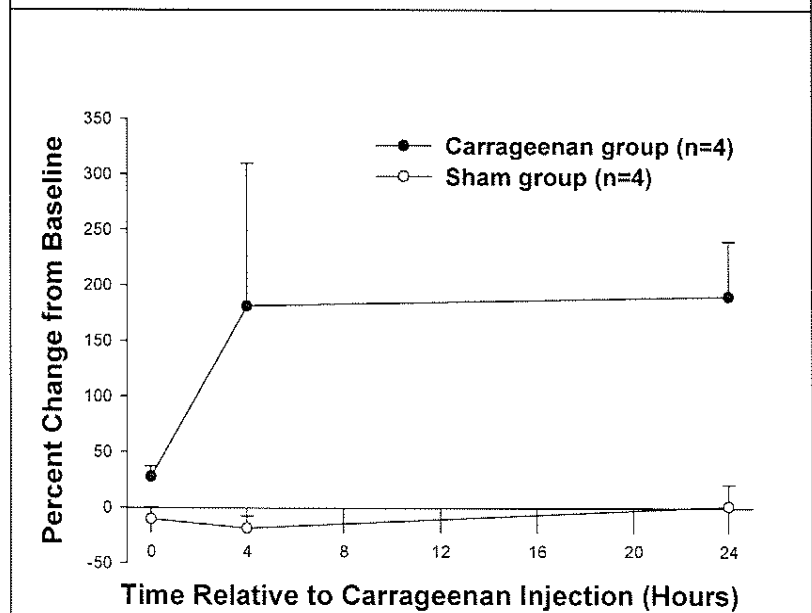


Figure 4. Change in Gnawing Function in the Masticatory Muscle Pain Model and Sham Group. Injection of carrageenan into the masseter muscle led to a change in gnawing function as measured by the dolognawmeter. There was no increase in gnawing time observed in the sham injected group that received inoculation of carrageenan vehicle.