The classic proof-of-concept model may bring versatility and cost effectiveness to later phase analgesic studies

**The Dental Impaction Pain Model: A Versatile Option in Analgesic Trials to Avoid Costly Late-Phase Failure**

By Todd M Bertoch, MD, CMO, JBR Clinical Research

Companies seeking to evaluate new analgesic entities face two critical early choices: which pain model to utilize and which research site(s) with which to partner. The vast array of pain models and sites available to sponsors can be daunting, and a mistaken choice in early development can lead to poor-quality data and ultimate project failure. This can be particularly devastating for start-ups or small sponsors with limited funding but also affects sponsors and contract research organizations (CROs) of any size. Combining the appropriate pain model with the most effective research site can prevent false negative results from forcing abandonment of a good product or false positive results from leading to costly failure down the line.

The modern Dental Impaction Pain Model (DIPM) is frequently considered the gold standard for proof-of-concept (PoC) studies. These are non-pivotal clinical trials that provide sponsors with data regarding efficacy and dosage before commencement of costly pivotal clinical trials. Less appreciated is the value of DIPM in all phases of drug development for a variety of molecules with analgesic properties. A brief look at the history
of the model shows how views of its value have evolved among analgesia experts over the decades.

**Background of the Model**

In 1971, when Dr. Stephen Cooper co-developed the DIPM, his motivation was to find better ways to test analgesic drugs to ultimately serve the complex, individual needs of postsurgical patients. The DIPM, which relies on postsurgical pain generated through extraction of third molars (aka “wisdom teeth”), became well established due to its high level of assay sensitivity, reproducibility, fast subject recruitment, and low cost compared to other acute postsurgical pain models. First proven valuable in evaluating nonsteroidal anti-inflammatory drugs (NSAIDs), over time, the DIPM became the most widely used acute pain model in the world, spawning hundreds of studies and leading to the development of many analgesic drugs with a variety of mechanisms of action.

Subsequently, some influential voices, reflecting an incomplete understanding of the DIPM, began to question the model’s adequacy to test the strongest analgesic drugs and its generalizability to other acute pain types and clinical scenarios. Some regulators and researchers were influenced by the perception that third molar surgery produces only mild pain, while other models, such as bunionectomy, were said to produce more severe and enduring pain. There followed a period when over-the-counter drug development dominated use of the DIPM, and companies developing more potent drugs used different and perhaps less efficient pain models.
Recently, the versatility of the DIPM has been reconsidered. Although not appropriate to evaluate every analgesic molecule or pain indication, the model offers multiple avenues for adaptability with the caveat that an established clinical research site employing experienced, trained staff is vital to trial success.

**Choice of the Right Model**

In deciding whether the DIPM – or any other pain model – is the right choice, it is necessary to weigh with care the many factors that contribute to a successful clinical trial. Judgment here is more important than ever because negative results from clinical trials have risen since the 1990s, even when the target molecules have known efficacy.⁵

An effective experimental pain model generates predictable pain in an understood physiological process and allows manipulations in the pain experience while minimizing analgesic confounders.⁴ Sponsors must look at cost, site experience, whether the pain stimulus is consistent, and whether there are potential confounders such as a non-homogenous patient population and use of concomitant medications.⁶

The chosen model must, at minimum:²

- Have sufficient assay sensitivity to discriminate against placebo and detect a treatment difference when the drug is efficacious
- Explore the full range of dosages for control and experimental drugs
- Yield reproducible results that can be extrapolated to the real world
While various postsurgical acute pain models possess these characteristics to some degree, the DIPM has many strengths that set it apart:²,⁶

- A standardized surgical procedure with little or no anesthesia to confound results
- An intense, predictable level of postoperative pain
- An assay sensitivity so precise that studies with up to six treatment arms have resulted in clear separation of the drugs from each other²
- A standardized effect size (difference in mean response in placebo and active comparator divided by standard deviation) higher than bunionectomy by 64%, joint replacement surgery by 122%, and soft tissue surgery by 202%⁴
- Fast recruitment and adequate numbers for trial enrollment in a homogenous population
- Ability to utilize single-site study centers to standardize trial procedures, reducing the variability seen with multicenter trials
- Enrollment of roughly equal numbers of men and women, unlike some other models such as bunionectomy, herniorrhaphy, and abdominoplasty
- Cost per subject that can be less than a quarter of that associated with some other popular, postoperative, acute pain models

The drug’s mechanism of action and type of pain to be treated should be carefully assessed before committing to a pain model.⁷ Although the DIPM may not serve as well for some narrow and specific pain indications, the model has been successfully used to study a wide variety of molecules, including NSAIDs, opioids, and non-traditional analgesics such as sodium
channel blockers. Data showing its versatility suggest to sponsors and regulators that the DIPM could be a far more broadly applied option in the future. Potential areas for future investigation include using the DIPM for PoC trials studying drugs designed to treat neuropathic pain or various other chronic pain conditions.

**The Model’s Versatility**

The DIPM is well known for studies in NSAIDs and opioid analgesics in which the model has shown remarkable reproducibility. Unparalleled for demonstrating assay sensitivity, investigating dose ranging, and assessing onset of analgesia in single-dose studies, the DIPM is readily adaptable to other uses, including:

- Correlations of pharmacodynamics to pharmacokinetics
- Pretreatment for surgical pain
- The onset, peak effect, and duration of analgesia in multi-dose acute pain studies lasting up to 48 hours

It is critically important to design the study protocol to accommodate the expected efficacy of the experimental and control drugs. To investigate high-efficacy analgesics using the DIPM, one must ensure that the protocol is designed to optimize the postsurgical pain experience. This experience can be influenced by varying both the number and type of impacted teeth extracted. The DIPM is one of the few acute pain models in which subjects can be pre-selected through X-rays of the dental impaction to either elevate or lower the postsurgical pain experience. This method effectively tailors the clinical trial to the anticipated potency of the experimental drug.
The DIPM can also be considered for prodrugs and other drugs with slow onset or unique mechanisms. In many respects, the DIPM is ideally suited to evaluate drugs designed as pretreatment to delay or minimize postsurgical pain. This could herald a new research direction in line with calls for multimodal perioperative methods that improve patient outcomes.\(^8\)

Evidence suggests that results are generalizable across a variety of pain states. Studies comparing the same treatments demonstrate that the results from the DIPM closely mirror those from general surgery, OB–GYN surgery, and bunionectomy.\(^2\) Historically, a successful PoC study using the model has predicted successful Phase 3 studies across several other acute pain models for that test compound.\(^4\) Equally as important, when the PoC in the DIPM finds minimal or no efficacy for the test drug compared to placebo, the experimental drug is very unlikely to perform better in other acute pain models.

As Cooper and Desjardins concluded, “We are not aware of any general analgesic drug, NSAID or opioid, used for acute pain that was ineffective in the DIPM while effective in other acute pain models.”\(^2\)

**Choice of the Research Site**

The choice of research site is at least as important as the decision process around pain models. Clinical research sites vary widely in their experience, training, methodology, ability to recruit, and appropriateness of catchment populations. Together, these factors affect the quality of the data that are eventually produced.
Too often CROs and sponsors select sites on the basis of familiarity or past affiliation, without a proper understanding of the sites’ true capacities. Discerning CROs and sponsors should require that potential sites produce documented evidence of:

- Experienced research coordinators, trained in effective methodology
- Verifiable data demonstrating acceptable intra-subject pain reporting discordance\(^9\)
- Verifiable data demonstrating acceptable inter-subject pain reporting variability\(^9\)
- Real-time review of data to detect unexpected variability and enact timely interventions to protect ultimate data integrity
- Access to a population of ample subjects in the indication being studied
- A proven track record of publications in peer-reviewed journals

Elite sites, as study protocols grow ever more complex,\(^{10}\) provide ongoing data surveillance as well as feedback and input to ensure the most flawless possible protocol execution.

Enrollment capacity is a primary concern as sites frequently overpromise and under deliver. According to a Tufts University report, only 39% of clinical research sites meet pre-study enrollment targets, and 11% fail to enroll a single patient.\(^{11}\) Proven enrollment performance, effective marketing tools, a trusted reputation within the community, and a catchment population consistent with study requirements are all points sponsors should evaluate.
A few red flags to watch for when evaluating a site include signs that 1) research is only a side business to a busy (and harried) physician-based practice, 2) sites lack consistent, verifiable staff training, 3) the investigators have a lackluster or absent publication record in peer-reviewed journals, and 4) business interests appear always to be front and center rather than scientific concerns.

At the site level, analgesic clinical research is a sometimes elusive mix of art and science. The methodology used at established sites to obtain high-quality data is not easily replicated on a part-time basis by a distracted physician group driven by financial considerations.

**Expertise and Experience**

An analgesic molecule may be efficacious in the population and indication studied; however, if the research investigators and staff lack expertise and training, the result may still be a costly false negative. A critical, often overlooked, predictor of success is the experience of the operating surgeon.

Experienced surgeons are skilled in manipulating surgical and postsurgical pain levels to demonstrate efficacy when a molecule is truly efficacious. A surgeon seasoned and expert in DIPM research understands the need for adequacy and consistency of elicited postsurgical pain among multiple and varied patients. The nuances of the surgical procedure required to maximize assay sensitivity of the model are learned over many years and are difficult to replicate dependably by most oral surgeons.
Research staff training should be in line with the IMMPACT recommendation to use only trained study personnel and standardized pain assessment methods in analgesic clinical trials. Self-funded pilot studies for training and model validation are a definite plus at the site level.

One reason the DIPM’s benefits in sensitivity and cost-effectiveness may be extended to a variety of postsurgical analgesic investigations is because superior research coordinators and staff can capture high-quality data and minimize confounders. Methodology is precise and includes knowing when to administer study medication and, if necessary, rescue medication. Mistakes in timing can make all the difference in a trial’s success or failure. For this reason, self-funded training of coordinators and staff featuring real patients is a hallmark of the best analgesic research sites.

**Conclusions**

Recognition of the DIPM as an effective, versatile, comparatively less expensive acute pain model is on the rise. Although not appropriate for every clinical pain trial, the DIPM’s profile is increasing for studies not previously associated with it thanks to its fast acquisition of high-quality data at significant cost savings. Data demonstrate that the model has value in evaluating a variety of pain states and analgesic molecules for the lifecycle of the drug. Research sites with experienced, trained staff are best prepared to minimize confounders and maximize results.
JBR Clinical Research

JBR Clinical Research, a CenExel Center of Excellence, has three decades of leadership in the acute analgesic research industry. Headquartered in Salt Lake City, Utah, with a database of 80,000 subjects, JBR partners with clinical trial sponsors and contract research organizations for accurate, results-driven clinical research studies. Three areas of particular expertise are:

- **Pilot studies:** conducted at the company’s own expense to train study coordinators with real patients and drugs
- **Methodology:** training performed in many aspects of trial conduct, including pain assessment, to capture accurate results
- **Data surveillance:** performed regularly in house to safeguard quality of data, flag outliers, and identify problems so they can be addressed before a study can be derailed

Along with retaining the contract of protocol development pioneer, Dr. Cooper, and other experts, JBR retains board-certified on-staff physicians and mid-level providers. JBR is recognized as the world’s premier dental pain study site and a top U.S. hard and soft tissue analgesic research site. Visit [https://www.jbrclinicalresearch.com/](https://www.jbrclinicalresearch.com/).

References


