



November 14, 2018

Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
White Oak Campus
10903 New Hampshire Ave.
Bldg. 31
Silver Spring, Maryland 20993

Re: **Docket No. FDA-2018-N-3479**; Anesthetic and Analgesic Drug Products Advisory Committee; Response to Request for Comments

Dear Dr. Gottlieb:

On behalf of the American Society of Anesthesiologists (ASA) and our nearly 53,000 members, I am writing in response to the above captioned Federal Register Notice regarding the Anesthetic and Analgesic Drug Products Advisory Committee's meeting to assess opioid analgesic sparing outcomes in clinical trials of acute pain. As experts in acute pain medicine, physician anesthesiologists have experience implementing best practices for *surgical acute pain* management, such as opioid sparing techniques that are based on the foundation of multimodal analgesia and can provide unique insight into clinical trial design.

ASA recommends that clinical trials for surgical acute pain focus on patients undergoing elective surgeries and measure outcomes by functional improvement in the patient and their quality of life. Clinical trials of acute surgical pain should:

- Examine utilization of non-opioids and multimodal approaches for postoperative pain management;
- Focus on preventing the transition of acute to chronic pain after surgery;
- Address adverse events related to opioid use in the perioperative period; and
- Study opioid induced hyperalgesia (OIH).

As stakeholders continue to address the opioid crisis that's plaguing the nation, the perioperative period is a critical opportunity. Because the surgical experience can be a patient's first exposure to opioids, for some patients, that exposure can ultimately lead to opioid abuse and misuse. Physician anesthesiologists have the unique knowledge and expertise to develop and utilize pain control alternatives that can reduce patient exposure to and use of opioids during surgery and at discharge. The severity of surgical postoperative pain is varied, and an integrated multidisciplinary pain discharge program is crucial for high-quality patient care. Physician anesthesiologists work with surgeons to provide pain control that uses alternative opioid pain relief techniques and protocols such as regional anesthesia and other analgesics as part of a multimodal approach to reduce the use of, and reliance on, opioids during a procedure

or surgery and at discharge. Clinical trials in acute surgical pain can provide the necessary data and evidence to ensure these practices are carried out in hospitals throughout the nation which can be a very important tool to reduce the opioid crisis.

Multimodal Analgesia and Alternatives to Opioids: Outcomes

Opioid-sparing techniques are recognized as an important component for postoperative pain management and should be the basis for any clinical trials on acute surgical pain. During surgery, anesthesiologists use regional anesthesia and analgesia to numb a precise part of the body having surgery, with injections utilizing ultrasound, such as nerve blocks. Current literature provides evidence that utilizing multimodal analgesia with non-opioids decreases opioid use post-operatively up to 30-40%.¹ Clinical trials on acute pain should aim to not only decrease opioid utilization during surgery, but also examine opioid utilization after discharge and examine the long-term outcomes of these patients. Clinical trials exist that demonstrate effective multimodal analgesia can improve range of motion of the knee at three-months, following total knee replacement surgery.²

Preventing the Transition from Acute to Chronic Pain

Over the last decade, there has been a greater recognition of the problem of chronic post-surgical pain. These patients that develop chronic pain from surgery have frequent physician visits and also end up chronic opioid users. Yet, we still do not fully understand the phenomenon. Current practice demonstrates that some surgeries can lead to the development of chronic pain. For example, incidence of acute to chronic pain is higher for patients undergoing an amputation, thoracotomy, total knee replacement or hernia. Additionally, patients with a pain condition prior to having surgery, such as fibromyalgia, has been thought to contribute to the development of post-surgical chronic pain.

Because this issue is so complex, and more information is necessary, clinical trials on decreasing the incidence of transition from acute to chronic post-surgical pain should be studied. Although it is a consequence of surgery for some patients, future research will help identify specific preoperative risk factors that explain why some patients develop post-surgical chronic pain. Perhaps by recognizing the problem, physicians can better identify these patients and improve strategies for minimizing risks preoperatively.

Decrease Adverse Events

It is well established that there are risk factors associated with opioids and patients undergoing surgery exposed to opioids might experience adverse events. Such events include nausea, vomiting and constipation, as well more severe but rare complications like respiratory depression and death. Multimodal analgesia has proven to result in better outcomes for patients and decrease adverse events. Therefore, clinical trials on acute pain should focus on implementing opioid-sparing techniques to decrease adverse events. Rare but severe

¹ Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management with Nonopioid Analgesics and Techniques: A Review. *JAMA Surg.* 2017;152(7):691–697. doi:10.1001/jamasurg.2017.0898

² Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of Perioperative Administration of a Selective Cyclooxygenase 2 Inhibitor on Pain Management and Recovery of Function After Knee Replacement: A Randomized Controlled Trial. *JAMA.* 2003;290(18):2411–2418. doi:10.1001/jama.290.18.2411

complications need a large sample size (thousands of patients) to be studied. Only through national initiatives can these measures be examined and improved upon.

Opioid Induced Hyperalgesia (OIH)

Opioid-induced hyperalgesia (OIH) can occur with patient exposure to opioids during surgery, thereby resulting in the patient becoming more sensitive to pain. The type of pain experienced can be the same as the underlying pain or different from the original underlying pain. Though a recognized problem, there is very little evidence about the prevalence OIH. Yet, it's thought that OIH might contribute to why some patients become desensitized to opioids. Clinical trials on acute pain should examine OIH to gather new information on the mechanism and physiology, as well as examine the factors that lead to OIH, and effective strategies for preventing, reversing, or managing OIH.

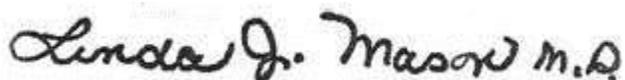
Clinical Trial Outcomes: Functional Improvement and Quality of Life

A successful clinical trial on acute pain will measure outcomes by the functional improvement in patients and their quality of life. Utilizing opioid-sparing techniques, including multimodal analgesia, should result in better patient outcomes. Factors to consider include pain scores achieved, nausea and vomiting, joint range of motion, sleep disturbance, patient satisfaction with analgesia, and hematologic and coagulation parameters. Patient quality of life is also important and clinical trials should factor-in the patient's physical, social and psychological wellbeing post-surgery. This goes beyond whether patients return to work following surgery and overall mobility but focuses on whether the patient has, for the most part, returned to life-as-normal.

Conclusion

ASA appreciates the opportunity to provide feedback in response to the FDA's request for comments on clinical trials in acute pain. The Society welcomes the opportunity to work with the agency on this topic and offers the organization and its members as a resource. Thank you for your time and consideration; please do not hesitate to reach out to ASA Pain Medicine and Federal Affairs Manager, Ashley Walton, J.D., with any follow-up questions via email at a.walton@asahq.org or by phone (202-289-2222).

Sincerely,



Linda Mason, M.D., FASA
President
American Society of Anesthesiologists