Opioid Sparing: Prescribing Less is Insufficient

Chronic and post-surgical pain that opioids are intended to alleviate have been offset by a host of societal pains stemming from the prevalence of opioid use disorder and related overdose deaths. In 2018, more than 9.9 million individuals misused prescription pain relievers, and the Centers for Disease Control and Prevention (CDC) estimates that more than 230,000 deaths have been attributed to prescription opioid overdoses since 1999[1].

Long-term opioid use often begins with treatment of acute pain and pain after surgery. Among those prescribed at least one day of opioids, the probability of continued use at one year is 6% – and increases to 13.5% for persons whose first episode of use was for eight days or longer[2]. More than 2 million individuals may transition to persistent opioid use following elective surgery each year[3]. The Council of Economic Advisers (CEA) estimated that the cost of this crisis in 2018 alone – in terms of the value of lost lives, increases in healthcare and substance abuse treatment costs, increases in criminal justice costs, and reductions in economic productivity – exceeded $695 billion. Indeed, the CEA projected that the cost of the opioid crisis would top more than $2.5 trillion over the four years between 2015 and 2019[4].

Yet chronic and acute physical pain often requires treatment with strong analgesics. A treatment with opioid-sparing benefits could help mitigate the risks associated with opioids in one or more ways:

- By decreasing the dose of an opioid
- By decreasing the total number of opioid doses
- By decreasing opioid-related side-effects
- By not requiring the use of an opioid at all

The one requirement linking all these options is this: the opioid-sparing therapy must not diminish the level of analgesia obtained.

"Opioid-sparing" as an elusive claim

Given the range of criteria that might be suitable for an opioid-sparing claim of a potential new treatment, clinical development options at first blush appear to be plentiful. However, regulatory sentiments regarding opioid-sparing indicate an uncertain evidentiary bar. There is currently no agreed upon definition of what constitutes "opioid sparing" and members of the Anesthetic and FDA's Analgesia Drug Products Advisory Committee (AADPAC) are largely in agreement that there is no evidence to support a broad label like "opioid-sparing"[5].

Indeed, the FDA recently noted only two products – Cumberland Pharmaceuticals' Caldolor® (IV ibuprofen) and Mallinckrodt PLC's Ofirmev® (IV acetaminophen)[6] – whose labels include opioid-sparing language, and that language is not standardised. Caldolor, approved in 2009, is indicated in part for the "management of mild to moderate pain as an adjunct to opioid analgesics." Ofirmev, approved in 2010, has similar labelling although for moderate to severe pain. Interestingly, guidance from 2014 (now retired) never noted how to establish an opioid-sparing labelling claim, noting only that it could be a suitable outcome measure.

What became clear across AADPAC meetings held in 2018 was that merely showing that a non-opioid product results in reduced use of an opioid in a placebo-controlled trial is not enough to allow a sponsor to promote a drug for such a benefit[6]. This observation occurs in AADPAC's review of Pacira BioScience's injectable local anaesthetic Exparel® (bupivacaine liposome injectable suspension)[6]. The application under review was for an expanded label for Exparel with a new nerve block claim as well as a revision of its existing infiltration claim. Although the requested indication did not include opioid-sparing language, the committee suggested the inclusion of long-term longitudinal data showing not only a "reduction in opioid use" *but also* "functional outcomes or other clinical benefits"[6]. The suggested range of options for demonstrating a beneficial functional outcome presents a mosaic of potentially informative development activities:

- Significant reductions in the amount of opioids required in the first 72 hours post-operatively
- Reduction in opioid-associated adverse events
- Complete elimination of the use of opioid drugs
- Decrease in the amount of opioids used over time
- Decreased rate of addiction
- Cessation of opioid usage sooner in pain management cases
- Decrease in pain intensity.

Thus, a claim that a product simply decreases the dose, frequency, or length of opioid use in a patient population does not by itself appear to support the inclusion of opioid-sparing language on a label – just that *less* opioid in and of itself is insufficient. Rather a product must demonstrate a *significant* reduction in dose, frequency, or length of opioid use. In addition, and most importantly, it must show functional outcomes or other clinical benefits, such as reduction in pain, reduction in opioid-related adverse events (e.g., sedation, constipation, nausea, vomiting), and reduction in the incidence of opioid dependency.

These ideas were amplified at an additional AADPAC meeting later in 2018[5]. Part of an unresolved challenge in demonstrating an opioid-sparing effect arises from an inability to quantify how much of a reduction in opioid use is clinically meaningful. Furthermore, quantified reductions may be difficult to achieve in real-world practice due to individual patient factors that depend on clinical circumstances. For example, it has not been established that opioid sparing in a hospital setting translates into sustained benefit after discharge. Somewhat counterintuitively, members of the research community may express concern that broadly labelling a medication as "opioid sparing" could result in unintended consequences, including overuse of the medication, inappropriate prescribing, and lack of comparable efficacy in patients[5].

Given the incomplete patchwork of regulatory and subject matter expert sentiments, there is currently no guidance for drugs claiming opioid-sparing effects[7,8], and the clinical target remains somewhat elusive vis-à-vis study methodology and programme design. As noted above, opioid-sparing benefits in the short term need to show not only equivalent reduction in pain, but also the absence of opioid-related adverse events and improvement in functional outcomes[9], which sets an ambitious threshold for programme success.

Creating a Research Standard

As a consensus develops on the utility of opioid-sparing claims in the future, developers and their study partners should proactively consider from an early date the development of hypotheses relating to the impact of an investigational product on severity and pattern of adverse events, opioid consumption, functional outcomes, and overall impact on healthcare utilisation both in the short and long term. The data generated by studies examining these questions may be useful in an opioid-sparing application later, and in some respects a successful application of the method will establish a standard by which opioid-sparing therapeutics could subsequently be evaluated.

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