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Research approaches for evaluating opioid sparing in clinical trials of acute and chronic pain treatments: IMMPACT recommendations

Jennifer S. Gewandter, PhD, MPH[a,*], **Shannon M. Smith, PhD**[a], **Robert H. Dworkin, PhD**[a], **Dennis C. Turk, PhD**[b], **Tong Joo Gan, MD**[c], **Ian Gilron, MD**[d], **Sharon Hertz, MD**[e], **Nathaniel P. Katz, MD**[f], **John D. Markman, MD**[a], **Srinivasa N. Raja, MD**[g], **Michael C. Rowbotham, MD**[h], **Brett R. Stacey, MD**[b], **Eric C. Strain, MD**[g], **Denham S. Ward, MD PhD**[a], **John T. Farrar, MD PhD**[i], **Kurt Kroenke, MD**[j], **James P. Rathmell, MD**[k], **Richard Rauck, MD**[l], **Colville Brown, MD**[m], **Penney Cowan**[n], **Robert R. Edwards, PhD**[k], **James C. Eisenach, MD**[o], **McKenzie Ferguson, PharmD**[p], **Roy Freeman, MD**[k], **Roy Gray, PhD**[q], **Kathryn Giblin, MD**[r], **Hanna Grol-Prokopczyk, PhD**[s], **Jennifer Haythornthwaite, PhD**[g], **Robert N. Jamison, PhD**[k], **Marc Martel, PhD**[t], **Ewan McNicol, PharmD**[u], **Michael Oshinsky, PhD**[v], **Friedhelm Sandbrink, MD**[w], **Joachim Scholz, MD**[r], **Richard Scranton, MD**[x], **Lee S. Simon, MD**[y], **Deborah Steiner, MD**[z], **Kenneth Verburg, PhD**[aa], **Ajay D. Wasan, MD**[ab], **Kerry Wentworth, BS**[ac]

[a]University of Rochester Medical Center, Rochester, NY, USA

[b]University of Washington, Seattle, WA, USA

[c]Stony Brook School of Medicine, Stony Brook, NY, USA

[d]Queens University, Kingston, Ontario, Canada

[e](Formally) U.S. Food and Drug Administration, Silver Spring, MD, USA

[f]WCG Analgesic Solutions, Wayland, MA, USA

[g]John's Hopkins School of Medicine, Baltimore, MD, USA

[h]University of California San Francisco, San Francisco, CA, USA

[i]University of Pennsylvania, Philadelphia, PA, USA

[j]Indiana University School of Medicine, Indianapolis, IN, USA

[k]Brigham and Women's Hospital / Harvard Medical School, Boston, MA, USA

[l]Carolinas Pain Institute, Charlotte, NC, USA

[m]Innocoll, Athlone, Ireland

[n]American Chronic Pain Association, Rocklin, CA, USA

[o]Wake Forest School of Medicine, Winston-Salem, NC, USA

[*]Corresponding author: Jennifer S. Gewandter, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave, Box 604, Rochester, NY 14642, 585-276-5661, (f) 585-244-7271, Jennifer_gewandter@urmc.rochester.edu.

10.Conflict of interest

The authors have no conflicts of interest directly related to the content in the manuscript.

[p]Southern Illinois University Edwardsville, Edwardsville, IL, USA

[q]GW Pharmaceuticals, Carlsbad, CA, USA

[r]Biogen, Cambridge, MA, USA

[s]University at Buffalo, Buffalo, NY, USA

[t]McGill University, Montreal, Canada

[u]MCPHS University, Boston, MA

[v]National Institutes of Health, Bethesda, MD, USA

[w]U.S. Department of Veterans Affairs / George Washington University, Washington, DC, USA

[x](Formally) Pacira , Parsippany, NY, USA

[y]SDG LLC, Cambridge, MA, USA

[z]Sarepta, Cambridge, MA, USA

[aa]Pfizer, NYC, NY, USA

[ab]University of Pittsburgh, Pittsburgh, PA, USA

[ac]Flexion Therapeutics, Burlington, MA, USA

1. Introduction

Randomized clinical trials (RCTs) have demonstrated the efficacy of opioid analgesics for the treatment of acute and chronic pain conditions [8, 28] and for some patients, these medications may be the only effective treatment available. Unfortunately, opioid analgesics are also associated with major risks and adverse outcomes, including the development of opioid use disorder (OUD), overdose fatalities, respiratory depression, falls, and other central nervous system, gastrointestinal, endocrine, and immune effects [5, 19, 37, 44, 53, 54, 70, 79, 80]. In addition, individuals in the community who have not been prescribed these medications can gain access to a family member or friend's prescription opioids [13], putting them at risk for OUD and overdose.

The adverse outcomes associated with opioid analgesics have prompted efforts to reduce their use in the treatment of both acute and chronic pain. A variety of interventions have the potential to reduce opioid use and dosages, including existing and novel medications, devices and smartphone applications (apps), psychosocial and physical treatments, and treatment guidelines and educational initiatives. A number of trials evaluating the effects of such interventions on the use of opioid analgesics for acute and chronic pain have been conducted [21, 42]. However, these clinical trials have differed greatly in their objectives, research methods, and outcome measures; which hinders the development of evidence-based treatment recommendations and application of the results of RCTs to clinical practice.

Opioid-sparing interventions are intended to reduce opioid use and in turn reduce opioid-associated risks and adverse outcomes, either in patients with acute or chronic pain or in the wider community. It is important to emphasize that opioid-sparing interventions should

not result in unacceptable increases in pain or pain interference in important domains (e.g., sleep, function, mood). Opioid-sparing interventions could involve policies, guidelines, or education campaigns focused on limiting opioids in the community; however, societal interventions will not be considered in this paper. The term opioid sparing can be used to describe multiple concepts of interest and opioid-sparing interventions [68], and thus there is no one accepted definition of opioid sparing. The recommendations presented in this article are based on the following definition of an opioid-sparing intervention, which reflects the meeting consensus discussions: Any intervention that (1) prevents the initiation of treatment with opioid analgesics, (2) decreases the duration of such treatment, or (3) reduces the total dosages of opioids that are prescribed for or used by patients, all without causing an unacceptable increase in pain. Although not technically "opioid-sparing," this article will also address trials that aim to reduce opioid-related adverse outcomes (without increasing opioid dosages).

In this article, we discuss considerations and present recommendations for clinical trials of opioid sparing, including those regarding study objectives, populations, research designs, outcomes, and interpretation of results. Although one major benefit of decreasing the number of prescription opioids in circulation would likely be a decrease in opioid-use disorder and opioid-related overdose deaths in the community, this article will not address these outcomes. We conclude with an overview of issues that require additional investigation and that are important elements of an agenda for future research.

2. Methods

An Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus meeting comprised of participants from universities, government agencies, industry, and patient advocacy organizations was held to discuss research methods for clinical trials with opioid-sparing objectives. Participants were selected on the basis of their research, clinical, or administrative expertise relevant to opioid analgesics or clinical trials of pain treatments and were mainly from the US, with representation from Canada and the UK. The meeting was designed to reflect a broad representation of relevant disciplines and perspectives while limiting the size to promote productive and efficient discussion. The recommended considerations presented in this article are applicable to multiple treatment modalities, including pharmacologic, device, physical, and psychological interventions.

We conducted a focused background review of articles reporting RCTs for the treatment of acute or chronic pain that included at least one outcome related to opioid sparing as defined above to inform the meeting and the development of recommendations. The methods and results of this review are provided in the Supplement. We chose a narrow search strategy (i.e., the Title or Abstracts of the articles were required to include the term "opioid sparing" to target trial reports that sufficiently prioritized opioid sparing). In order to supplement our search, the consensus meeting planning committee was asked to identify acute and chronic pain RCTs with opioid sparing outcomes. We evaluated the study objectives, intervention types, control types, inclusion and exclusion criteria, primary and secondary/exploratory outcomes, method of assessing opioid dosage, and reporting of clinical relevance used in sample size determination or the interpretation of study results.

To facilitate discussion at the consensus meeting, selected participants delivered presentations on pertinent topics. These presentations and the meeting transcript are available at: http://www.immpact.org/meetings/Immpact21/participants21.html. The considerations and recommendations presented in this article are based on the background review, meeting presentations and discussions, published systematic reviews [26, 27, 43, 73], and iterative revisions of drafts of this article by the authors.

4. General considerations for clinical trials

4.1. Study populations

Potential opioid sparing interventions can be studied in healthy volunteers using evoked pain stimuli to examine the effects of an intervention on opioid dosages and adverse events (AEs), especially measures of respiratory depression (i.e., hypercapnia and hypoxia). Postoperative opioid-induced respiratory depression may cause significant morbidity and mortality and evaluating the effect of an opioid sparing treatment on respiratory depression in healthy volunteers can be a valuable component of early phase trials, especially if the opioid sparing intervention is novel and might itself interfere with respiratory function. The advantages involve efficiencies in participant recruitment and in the study duration needed to obtain a preliminary understanding of potential opioid sparing benefits; for example, does the addition of an anti-inflammatory drug result in sufficient reduction in opioid dosage to decrease respiratory depression in healthy volunteers [45]? However, the disadvantage of trials conducted in healthy volunteers is that the noxious stimuli are transient and the information they provide regarding efficacy in the patient populations for which the treatment is intended may be limited. The safety information may also be limited given that patients are more likely to have comorbid conditions and concomitant medications. Additionally, investigators should consider ethical considerations related to giving potentially-addictive opioids to healthy volunteers.

Despite the importance of such early proof-of-concept studies, our focus will be on clinical trials of opioid sparing in patients with acute and chronic pain. The major opioid sparing objectives of RCTs in patients with, for example, post-surgical or post-traumatic acute pain would include decreasing opioid dosages or eliminating opioid usage at or shortly after discharge, and limiting outcomes, including the exacerbation or development of misuse and abuse while maintaining adequate pain control. A main advantage of focusing on the acute pain population is the short-term, efficient follow-up period that limits the risk of missing data, which is often a significant challenge in longer-term trials in the chronic pain population. The major opioid sparing objectives of chronic pain RCTs would include preventing initiation of opioid use, lowering dosages or discontinuing opioid therapy in patients currently receiving opioids, and limiting adverse outcomes, including misuse, abuse, OUD, and overdose while maintaining pain control. Challenges in this population include measuring at-home use of opioids (see Section 4.3a) and increased risk of missing data than in the acute setting. Electronic, rather than paper, diaries with prompting notifications can be considered to decrease missing data [35, 64].

Prognostic enrichment through the use of selected entry criteria can be used to increase the statistical power of trials aimed at preventing initiation of opioid use or adverse outcomes

associated with opioids [67]. For example, if a trial aims to evaluate the incidence of opioid abuse associated with use of an opioid, enrolling patients with risk factors for developing misuse or abuse (e.g., psychiatric comorbidity [73]) may decrease the number of participants required for the trial to have adequate statistical power and increase the generalizability of the trial results to the population most at risk. However, ethical implications should be considered in cases where a trial involves assigning participants to an opioid treatment group.

If the objective of an opioid sparing RCT is to decrease post-operative nausea and vomiting (PONV), enrolling patients who have a history of PONV or motion sickness will increase the trial's statistical power and generalizability to the most relevant populations. If evaluating post-operative respiratory depression is the goal, inclusion of patients with obstructive sleep apnea or those who take concomitant medications with central nervous system depressant properties (e.g., benzodiazepines) could be considered. For all of these examples, anticipated increases in study efficiency would need to be weighed against the potentially increased risks to participants.

4.2. Addressing pain control in opioid sparing trials

As noted previously, when evaluating the efficacy of an opioid sparing intervention, it is important to measure whether pain increases substantially as an unintended consequence of decreasing opioid use. These two important domains (i.e., pain and opioid sparing) can be incorporated in the primary analysis of a clinical trial by using multiple primary endpoints with adjustment for multiplicity or by generating a single composite endpoint that includes both domains. If evaluating opioid and pain endpoints, the trial objective could be to demonstrate superiority on the opioid sparing outcome and non-inferiority for the pain outcome with a pre-specified margin for acceptable increase in pain. In this case the two outcomes would be treated as co-primary outcomes, both requiring a statistically significant result for the trial to conclude efficacy. A non-inferiority analysis requires a pre-specified difference in pain between groups that would be acceptable to conclude non-inferiority (i.e., the non-inferiority margin) [23, 69]. Identifying a minimally clinically meaningful difference between groups could be challenging because it cannot be informed by asking patients what difference in pain from baseline would be meaningful to them [20]. Decisions regarding what is a clinically meaningful difference should be based on the goals of the clinical trial and the perspectives of relevant stakeholders. For example, in an early phase trial with smaller numbers, investigators may wish to make a non-inferiority threshold more liberal in order to prevent abandoning a potentially effective therapy too early. However, during a larger phase 3 study, a smaller margin would be used to ensure that significant worsening of pain does not occur. For opioid sparing RCTs, a somewhat larger non-inferiority margin than what might be used for other trials could be considered because of the potentially large benefits of decreasing adverse outcomes related to opioid use (e.g., side effects).

The second option, that is, use of a composite endpoint of pain and opioid sparing as the primary endpoint, has the advantage that both domains are assessed within each participant, rather than evaluating each domain separately, therefore, more comprehensively evaluating

well-being of the participants [29]. This has been referred to as using endpoints to analyze patients rather than patients to analyze endpoints [24]. Multiple methods are available to generate composite endpoints from two different domains. The most common method to create composite endpoints used in the pain field involves defining participants as "responders" or "non-responders" based on the change in their status on each domain during the trial. For example, a "responder" for a chronic pain RCT could be defined as a participant whose pain did not increase by more than 20% and whose opioid dosage decreased by at least 50%. Examples of "responder"-based composite endpoints that include pain, physical function, and patient global assessment, and other domains have been proposed for rheumatoid arthritis [25], chronic low back pain [6, 58], and neuropathic pain [51].

Other methods involve rank-based approaches. For example, the O'Brien Rank-Sum method ranks participants on their performance on different domains and then averages the separate rankings to determine an overall rank for each participant [49]. An adaptation of this approach that combines pain scores and opioid consumption has been proposed for acute pain trials [57]. Another ranking approach is the desirability of outcome ranking (DOOR) method in which investigators develop an evidence-based ranking scheme based on performance on various outcome domains [24].

Patients should be consulted regarding their priorities for opioid sparing when designing composite endpoints. Priorities regarding dosages, side effects, and amount of pain control they may be willing to sacrifice to reduce opioid use should be investigated. This research could be used to design endpoints that are appropriate for as many patients as possible or an endpoint that can be personalized for each participant at the beginning of a trial (e.g., a participant-specific responder definition that includes a pre-specified decrease in a specific opioid-related adverse outcome with up to a specific increase in pain that the participant is willing to tolerate) [29]. One disadvantage of the composite outcome approach is that, depending on how the endpoint is constructed, significant results can be driven solely by one domain [29]. The exception to this disadvantage would be a "responder"-based composite endpoint that requires a substantial improvement on two domains or a substantial improvement on one domain and less than minimal worsening on another domain.

In addition to pain intensity, investigating the effects of opioid sparing on sleep, anxiety, depression, cognition, and function would be important secondary outcomes. Sensitivity analyses that investigate whether participants who decrease opioids and have increased pain, but also have improvements in these other domains are recommended. Section 5 discusses relevant study objectives for opioid sparing trials and specific design issues for each objective. Each of these objectives should include the component of maintaining adequate pain control and other clinically important domains; however, to avoid redundancies, the concepts covered in this section are not repeated in each of the sections below.

4.3. Outcome assessments

4.3a. Opioid consumption—Changes in opioid consumption and the rate of opioid discontinuation were the most common outcomes found in a systematic review of opioid sparing research [27] and the background review of opioid sparing RCTs that we conducted.

However, it is challenging to determine whether merely decreasing opioid consumption in the absence of improving opioid-related adverse outcomes is clinically meaningful, especially in the acute pain setting [46, 47]. Assessment of opioid consumption in acute pain trials in hospital settings is generally accomplished using automatically recorded patient-controlled analgesia (PCA) boluses or recorded directly by the research staff. These methods are generally highly reliable and associated with little missing data. However, it is important to consider that when using a PCA, the size of the bolus dose could affect the granularity of the opioid sparing data (e.g., larger boluses may make it difficult to detect smaller differences in opioid usage). Outcomes could include mean daily dosage or whether or how frequently an opioid was used in the days following a surgery or traumatic event. At-home assessment of opioid consumption for acute trials with follow-up that extends past the hospital stay or for chronic pain trials is less reliable. The most common method used in the clinical trials identified in our background review was self-report, which is known to often be inaccurate. Other options include pill counts, electronic dispenser caps, and electronic application-based monitoring systems [75, 76]. The advantages and limitations of methods used to measure medication use in clinical trials for pain can be found in the IMMPACT recommendations on data quality [30]. Outcomes for the post-hospital setting could include mean daily dosage, number of days requiring any opioid analgesia, total opioid dosage utilized over a particular study period, or frequency of opioid medication usage. If an outcome of a trial involves use of clinically prescribed opioids (i.e., not a standardized type and dose of opioid for the trial), it is important to consider the limitations of opioid conversion tables that are based largely on acute pain models [55].

When planning an RCT, defining what constitutes a clinically meaningful decrease in opioid consumption for individual patients with acute or chronic pain is not straightforward. Although the results of some studies have suggested that higher daily dosages of opioids are related to OUD and overdose deaths in patients with chronic pain [19, 80], available evidence does not make it possible to specify the percentage or absolute change in opioid dosages in either acute or chronic pain settings that would significantly change these clinically meaningful outcomes. While many experts believe that decreasing chronic use of high dosages of opioids to moderate or low dosages would likely be beneficial for patients from a harm perspective, no consensus has emerged regarding what constitutes a high dosage [18]. Given that most existing analgesic treatments have generally modest long-term effectiveness for many patients and that there are financial barriers to some non-pharmacologic interventions (e.g., psychosocial and physical therapy) [39], it is important to recognize that decreasing opioid dosages could actually worsen a patient's overall health status. Furthermore, the optimal dosage of opioids can be different for different people, depending on the severity of their pain, BMI, metabolism, sex, genetics, and opioid tolerance [17, 56]. Thus, until a better understanding of what opioid dosage reductions result in clinically meaningful benefits for patients emerges (see Section 7.2), opioid-related adverse outcomes should be included as secondary outcomes in all opioid sparing trials.

4.3b. Opioid-related adverse outcomes—As with any condition that includes multiple domains, investigations of adverse outcomes must determine whether to focus on the most clinically consequential outcomes (e.g., OUD, respiratory depression, falls) or the

most common (e.g., nausea or constipation) or a composite of several domains. As noted previously, relevant opioid-related adverse outcomes include, but are not limited to, nausea, constipation, dry mouth, dizziness, drowsiness, lack of energy, falls, difficulty passing urine, respiratory depression, endocrinopathy, altered immune function and post-operative infection, misuse, abuse, and OUD [5, 19, 37, 44, 53, 54, 70, 79, 80]. Decisions regarding which adverse outcomes are most consequential may be different for different populations (e.g., acute vs. chronic pain patients, older or younger patients, those who are or are not taking multiple other medications) and shaped by individual preferences. These decisions should be informed by input from patients, clinical experts, and any relevant literature (e.g., [65]).

Each adverse outcome could be measured separately using patient-reported outcome measures, clinician-reported outcome measures, or laboratory tests when appropriate. Both the frequency and severity of the adverse outcome, when appropriate, should be considered (e.g., mild infrequent nausea vs. severe common nausea). These separate measures could be combined using similar methods to those described below in Section 6.3. A patient-reported symptom inventory can also be used to assess multiple relevant symptoms simultaneously (i.e., as a single syndrome). For example, the Opioid-Related Symptom Distress Scale was developed to quantitatively assess post-operative opioid adverse outcome based on the frequency, severity, and distress caused by each component [4]. If using separate measures for each adverse outcome, investigators should pre-specify how each outcome will be analyzed and contribute to the interpretation of the trial results (i.e., as part of primary or secondary analyses). If using a composite endpoint, it is important to recognize that composites can be challenging to interpret, especially if some symptoms improve with the intervention while others worsen or some adverse outcomes are significantly more clinically impactful than others [29]. Sensitivity analyses should be conducted to examine changes in individual domains [22, 66].

5. Study objectives and research designs

The advantages and limitations of relevant potential objectives for opioid sparing trials in the acute and chronic pain setting are discussed in this section. Many of the considerations discussed are related to clinical trials aimed at preventing chronic opioid therapy and opioid-related adverse outcome, some of which are relatively uncommon (e.g., OUD). When research objectives include preventing relatively rare events, pragmatic trials and real-world data approaches (e.g., [14]) are important options that can supplement and inform the results of explanatory RCTs. These approaches, however, are outside the scope of this manuscript, which will focus only on phase 2 and 3 RCTs.

5a. Acute pain (Table 1)

5a.1. Does the intervention prevent use of opioid analgesics for acute pain that is usually managed with an opioid analgesic (e.g., after trauma or surgery)?—Preventing the initiation of treatment with opioid analgesics in patients with acute pain would not only prevent acute opioid-related adverse outcome, but remove the risk for potential longer-term opioid adverse outcome, including OUD and overdose. Thus,

the clinical relevance of this study objective is clear. The outcomes for such an RCT would be use of any opioid analgesics during a patient's inpatient stay or for their acute pain condition. In addition to pain intensity at rest, pain intensity with surgery/trauma-relevant activity [38] and post-operative sleep quality should be included for this objective along with all objectives that are evaluated shortly after surgery or trauma. In addition, mobility outcomes and adverse outcome related to decreased mobility (e.g., DVT or decreased peak respiratory flow [32]) should be considered for all acute objectives.

An advantage of preventing the use of opioids is that it is a dichotomous endpoint that is easy to interpret and has little chance for measurement error. One disadvantage is that it can be difficult to eliminate entirely the need for an opioid analgesic, especially for major surgeries and trauma. For such surgeries and traumas, reducing overall opioid consumption or eliminating the need for an opioid prescription at hospital discharge, as discussed below, may be more clinically relevant.

5a.2. Does the intervention reduce opioid dosages in patients with acute pain?—Considering the large numbers of surgeries that require post-operative analgesia and emergency and urgent care visits for acute pain (e.g., fractures, renal colic), this clinical trial objective is relevant from the perspective of decreasing the overall amount of opioids prescribed. However, it is not clear what magnitude reduction in short-term opioids would be necessary for a clinically relevant impact on patients. Although some studies demonstrate that higher daily dosages of opioids are related to the development of OUD and overdose deaths in patients with chronic pain [19, 80], little evidence is available to inform what percentage or absolute decreases in opioid dosages for acute pain would be clinically meaningful, not only for the acute phase but also with respect to longer-term adverse outcomes. This challenge is reflected in the fact that few studies identified in our background review discussed the clinical meaningfulness of the reductions in opioid use that were observed.

A main goal of reducing the dosages of short-term acute opioid consumption is to decrease short-term opioid-related adverse outcome. Although opioid dosage has the advantage of being an objective measure, reducing opioid-related adverse outcome (See Section 5a.3) may be a more clinically meaningful objective than reducing opioid consumption because adverse outcome can mostly be measured by asking participants directly. Relevant outcomes for RCTs that test interventions intended to reduce opioid dosages include total opioid consumption over a pre-specified number of days (e.g., from a PCA device).

5a.3 *Does the intervention reduce opioid-related* adverse outcomes *in patients with acute pain?—*Decreasing the incidence or severity of opioid-related adverse outcomes in the acute pain setting is arguably clinically meaningful because this is what affects participants' quality of life and safety. However, opioid-related adverse outcomes require decisions regarding which outcomes to evaluate and whether and how they should be combined into a meaningful composite endpoint. Unfortunately, few relevant studies are available upon which to base such decisions (see Section 6.2 for further discussion of this topic).

It is possible that an intervention that treats opioid-related adverse outcomes (e.g., nausea) could lead to increased opioid consumption if the side effect was limiting opioid consumption. Although we consider decreasing opioid-related adverse outcomes as part of the broad definition of opioid-sparing in this manuscript, if an intervention is accompanied by increased opioid consumption, it should not be considered opioid sparing. Thus, in trials that are designed to assess improvements in opioid-related adverse outcomes (see also Section 5.b.3), opioid consumption should be included as a secondary outcome and assessed using a composite outcome or non-inferiority approach similar to those proposed for analyzing pain in these trials in Section 4.2.

5a.4. Does the intervention eliminate the need for an opioid prescription at hospital discharge in patients with acute post-surgical or trauma pain who would usually require an opioid in this setting?—The rationale for this trial objective is the assumption that if patients do not leave the hospital with an opioid prescription they will be less likely to develop an OUD and less opioid medication will be available in the community. A large retrospective cohort study showed that patients who received an opioid prescription at hospital discharge were 3 times more likely to have an opioid prescription after 1 year than those who did not receive an opioid prescription at discharge [10]. The clinical and societal meaningfulness of avoiding opioid use after discharge is straightforward compared to assessing the value of opioid dosage reductions in the hospital. However, to our knowledge, there is no systematic prospective research that has examined whether receiving an opioid prescription at discharge is associated with significantly better functional outcomes than not receiving such a prescription. A related study objective would be to reduce or eliminate the number of participants needing a renewal opioid prescription shortly after hospital discharge, for example, at 2 weeks. This outcome may be more relevant for major surgeries or traumas for which leaving the hospital without a limited opioid prescription may be unlikely even with a moderately efficacious opioid sparing intervention.

Relevant outcomes for these RCTs include whether participants leave the hospital with an opioid prescription or filled the opioid prescription as well as pain measured after hospital discharge. Secondary outcomes could include physical function, mood, and overall quality of life. Hospital readmissions or emergency department visits for pain control within 30 days should also be considered. An advantage of this study objective is that missing data related to whether the participant received an opioid prescription should be negligible because it can be documented directly by the study staff.

5a.5. Does the intervention decrease the duration of opioid use after surgery or an acute pain problem for patients who would usually require an opioid in this setting?—The results of a recent analysis using claims data suggested that the durations of post-surgical opioid prescriptions were more strongly associated with opioid misuse than were the dosages [7]. Although these results should be interpreted with caution considering the retrospective nature of the study, they suggest that minimizing the duration of opioid use after surgery or an acutely painful trauma or illness may reduce opioid misuse and other adverse outcomes, supporting the clinical meaningfulness of this objective. For a

clinical trial with this objective, the major outcome would be the number of days of opioid use after discharge, as well as pain, physical function, and mood. Another relevant outcome is the number of refills the participant obtains. However, this outcome would require that the dosage and number of pills for each prescription refill is standardized for the study.

This trial would be similar to those intended to eliminate opioid prescriptions at discharge except that the follow-up duration would be longer. One disadvantage is that longer follow-up requires more resources and provides more opportunities for missing data. Another challenge for trials evaluating an intervention's effect on duration of opioid use after discharge is the need to measure home-based opioid usage. Advantages of evaluating the duration of opioid use are that continuous endpoints generally provide greater statistical power than dichotomous outcomes and that no decision is needed regarding the timing of acute endpoints (e.g., discharge or 1 week or 1 month post-discharge).

5a.6 Does the intervention reduce the incidence of opioid use 3 months after surgery or trauma in opioid-naïve patients who would usually require an opioid in this setting?—The clinical meaningfulness of this outcome is clear given that continued use of opioid analgesics beyond a few months after surgery or an acutely painful trauma or illness in patients who were not taking opioids at the time their acute pain began is clearly undesirable. One potential limitation of this study objective is that trends in opioid prescribing practices may limit the number of patients who are treated with ongoing opioid therapy [34, 63, 72, 81]. An RCT designed to test this study objective could therefore require a large number of participants to show that the intervention has further reduced opioid use beyond what could already be low levels at 3 months. A similar trial objective, but for patients using opioids for a chronic pain condition prior to surgery, would be to decrease the incidence of opioid dosages that are greater than pre-surgery dosages at 3 months after surgery. As with trial designs for testing other study objectives, relevant outcomes would include opioid use and dosages, pain, physical function, and mood, as well as adverse outcomes, including misuse and abuse.

5b. Chronic pain (Table 2)

5b.1. Does the intervention prevent initiation of opioid analgesics in opioid-naïve patients with chronic pain?—Eliminating the need for initiation of opioid therapy for chronic pain would certainly prevent opioid-related adverse outcomes. Whether a novel intervention prevents use of an opioid analgesic should be evaluated in an opioid-naive population for whom an opioid analgesic would likely be the next step for managing chronic pain (i.e., in those who have not responded to non-opioid analgesics or cannot tolerate them). One research design to evaluate this objective would be to randomize patients to the experimental intervention vs. placebo and evaluate the proportion of participants who utilize rescue opioid analgesia or the average dosage of rescue opioid analgesia used. To decrease variability in the outcome, investigators could consider standardizing use of opioid rescue medication (e.g., when pain ≥ 5 out of 10).

Another option would be to randomize participants to receive either an opioid, a putative opioid sparing (i.e., "opioid replacing") treatment, or placebo and measure the amount of

rescue analgesics that are used. Such an RCT would not only test whether the opioid sparing treatment could achieve comparable pain reduction to opioids for patients with refractory pain but could also examine whether the opioid sparing treatment is associated with fewer adverse outcomes and improved physical function and mood when compared to an opioid analgesic. The SPACE trial provides an example of such a trial, but did not include a placebo group.[41]

A more pragmatic approach would involve randomizing participants to the opioid-sparing intervention vs. placebo and evaluating the proportion of participants who are prescribed an opioid by their clinician. One challenge for such a design is that changes in prescribing practices appear to be decreasing the number of patients receiving opioids for chronic non-cancer pain [34, 63, 72, 81]. Thus, the outcome in this type of design may be relatively infrequent, leading to a large sample size requirement. Furthermore, clinical decisions regarding whether to prescribe opioids are based on multiple factors that will add variability to the outcome, leading to further increases in sample size requirements.

5b.2. Does the intervention decrease opioid dosages in patients managing chronic pain with an opioid analgesic?—Although the outcome of opioid-dosage is appealing because it is objective, it is difficult to interpret the clinical importance of decreases in opioid dosages given the lack of evidence available and the variability in the effects of different opioid dosages for different people. These important questions should be a focus of future research (see Section 7.2). The treatment goals for chronic pain patients using high dosages of opioids (e.g., >120MME) are likely different than for those using lower dosages (e.g., 30-50MME). Thus, including patients with relatively similar dosages in a trial could be advantageous when choosing a primary outcome. For example, for high-dosage opioid users, an appropriate goal might be to decrease dosages by at least 50%, whereas for low-dose opioid patients an appropriate goal might be to stop using opioids altogether. If including patients on high dosages, recruitment may become challenging as changes in prescribing practices continue to occur in response to changes in opioid prescription regulations and practice guidelines [34, 63, 72, 81].

Trials aimed at decreasing opioid dosages in patients managing chronic pain with opioid analgesia should specify the methods that will be used for opioid tapering and consider ethical implications related to aggressive or forced opioid tapering [16]. One option for opioid tapering in clinical trials is to allow participants to decide if, or when they should reduce their opioids. This approach would not include specific instructions or require participants to reduce their opioid dosages. Because participants may be hesitant to taper their opioid dosages because of fears of withdrawal or increased pain, an absence of instructions regarding when to reduce opioid dosages may make it difficult to detect differences in efficacy. For example, if participants in an active treatment group are hesitant to decrease opioids even if their pain is moderately better, the trial might not show a difference in opioid usage between groups. Instructing participants to decrease opioid dosages when specific pain intensities are reached would promote tapering with pain improvement and decrease variability of responses. Future research that systematically investigates the relative success of different opioid tapering strategies would inform trial design.

5b.3. Does the intervention decrease opioid-related adverse outcomes in patients managing chronic pain with an opioid analgesic and experiencing significant side effects?—For patients with chronic pain who receive adequate pain control from their long-term opioid therapy, the most clinically important outcome would arguably be to decrease adverse outcomes. Assessing opioid-related adverse outcomes rather than opioid dosages eliminates the challenge of identifying what constitutes a clinically meaningful decrease in opioid consumption. However, identifying a clinically meaningful reduction in opioid-related adverse outcomes also has challenges, including which opioid-related outcomes to evaluate and whether they should be combined into a composite endpoint. One approach would be to include only patients who are experiencing specific side effects (e.g., nausea or endocrinopathy) and measure that side effect as the primary outcome. Section 4.3b provides a further discussion related to assessing opioid-related adverse outcomes.

5b.4. Does the intervention prevent opioid misuse, abuse, or OUD in pain patients with chronic pain?—It is indisputable that preventing opioid misuse, abuse, and OUD [3, 59] are highly clinically meaningful outcomes for patients. One challenge for this study objective is that validated measures that can accurately identify opioid misuse, abuse, and OUD are limited [50, 60, 61]. Furthermore, identifying OUD may be challenging unless patients are weaned off of their opioids. A recent systematic review assessed the psychometric evidence to support various potential measures, and the authors concluded that of the reviewed patient-reported outcome measures, the Current Opioid Misuse Measure (COMM) [9] performed best for identifying current opioid misuse [43]. However, since the development of the COMM, the concept of opioid misuse has evolved such that opioid misuse and abuse are considered distinct domains [59], which are not distinguished by the COMM; thus, it does not provide a precise assessment of opioid misuse, abuse, and OUD. The Opioid Compliance Checklist (OCC)[36] is a brief self-report instrument that was recently developed to evaluate opioid misuse among patients with chronic pain on long-term therapy that could be used as an alternative to the COMM. An alternative approach to measure opioid misuse is a composite measure of self-report, clinician assessment, and urine drug testing (e.g., the approach used in [77]). Another large, prospective trial [1] used an abuse index based on DSM criteria [2] for misuse and abuse. However, further validation of such composite measures is required.

As with all prevention trials, an RCT designed to test an intervention to prevent opioid misuse or abuse will likely require more participants than a trial aimed at decreasing opioid consumption and likely require at least several years of follow-up, especially if the incidence of opioid misuse and abuse is low. However, at least one such large trial has been successfully completed, demonstrating feasibility [1]. According to a recent systematic review of studies including chronic non-cancer pain patients currently taking oral opioid analgesics, the average prevalence estimates for opioid misuse ranged from 21% to 29% and average rates of opioid addiction ranged from 8% to 12% [74]. Clinical trials designed to show statistically significant reductions in these percentages would require substantial numbers of patients. Thus, for this objective in particular, research methods involving real-world data may be particularly useful. The prevalence of opioid misuse and addiction

outcomes has been shown to be higher in patients with current illicit drug use or a history of substance abuse [26, 40]. Prevention in such patients would be of great clinical importance, and the sample size requirements for such RCTs would be smaller.

Another important consideration is that the range of prevalence estimates in studies of opioid misuse and abuse are highly variable (i.e., 0 to 81%) [26, 74]. Thus, the accuracy of the average estimates may be low, which could compromise the sample size determination. A blinded interim analysis to assess the overall incidence of the primary outcome is recommended to inform potential adjustment of the target sample size to ensure adequate statistical power [31]. Post-marketing studies of long-term use of extended-release opioids are currently being conducted to obtain better estimates of misuse, abuse, and OUD rates in patients with chronic pain [15], which will further inform the design of the RCTs discussed in this section.

6. Interpretation of results

6.1. Covariates and confounders

When conducting analyses related to opioid sparing, it is important to address the following variables, which may affect opioid consumption and opioid-related adverse outcomes, in the analyses: (1) age; (2) race/ethnicity; (3) socioeconomic status; (4) baseline opioid consumption; (5) baseline pain levels; (6) baseline use of other analgesics and pain treatments; (7) baseline anxiety, depression, obesity, pulmonary function, sleep, and function; (8) comorbid chronic pain conditions; and (9) duration and type of chronic pain being studied (for chronic pain trials). In addition, if the goal of an RCT is to evaluate opioid misuse, abuse, and OUD, risk factors for these adverse outcomes should be assessed and considered for inclusion in the analyses (e.g., history of substance use disorder, mental health comorbidities) [73].

6.2. Safety

If the intervention that is being evaluated is another analgesic medication, special attention should be paid to adverse outcomes that may occur from the combination of opioids and the putative opioid sparing medication. New or worsening opioid-related adverse outcomes could negate the benefits of a treatment even if opioid dosages, other opioid-related adverse outcomes, or a composite of opioid-related adverse outcomes are decreased. For example, a recent meta-analysis found that perioperative use of gabapentinoids was associated with lower post-operative nausea and vomiting, but more dizziness and visual disturbance [71]. In addition, retrospective studies suggest that concomitant gabapentin may increase the likelihood of post-operative respiratory depression and opioid-related overdose [12, 33, 78].

6.3. Non-study opioid analgesics and illicit drugs

Use of non-study opioids or other illicit drugs during the course of an RCT could affect opioid sparing and related outcomes. Urine drug testing (UDT) using sufficiently sensitive assays should be considered to monitor usage of such drugs, although UDT can only detect recently consumed drugs. In particular, cannabinoid use should be monitored given the recent increase in cannabinoid use for pain and suggestions that cannabis

and other cannabinoids can reduce opioid dosages for pain [11, 48, 52, 62]. Data from prescription monitoring systems could also be used to evaluate whether participants are getting undisclosed prescriptions from prescribers not associated with the study. Sensitivity analyses should investigate whether use of prohibited drugs potentially affected the trial results.

7. Research priorities (Table 3)

7.1. Identifying patient priorities for opioid sparing to inform development of opioid sparing outcomes

Evaluating why patients with acute and chronic pain would want to decrease or discontinue their opioid medications will provide an important foundation for developing content-valid measures of opioid sparing. This research should be performed with heterogeneous groups of patients of different ages, races, ethnicities, geographic locations, socioeconomic circumstances, and pain conditions and who have used opioids for different amounts of time. Interviews with their caregivers, who may observe different effects of opioids compared to patients who may be experiencing cognitive and emotional side effects are also recommended. Structured qualitative interviews with a smaller number of patients could be used to design a survey that is then distributed widely. The results of this survey would help to inform which types of adverse outcomes are most important to include in a measure of opioid-related adverse outcomes and also identify other important outcomes for opioid sparing trials.

A major question that should be addressed in such research is whether there is a minimal amount of increase in pain that is acceptable to allow for discontinuation of opioids and what magnitude of improvement in function, sleep, mood, or other outcomes might offset such an increase in pain.

7.2. Identifying clinically meaningful reductions in opioid dosages or prescriptions

Although decreasing dosages of opioids was the most common outcome in opioid-sparing RCTs in our background review, three-quarters of the reviewed articles did not comment on the clinical meaningfulness of the results. Future studies should investigate what dosage changes have a meaningful effect on patients. In the acute setting, such research could evaluate the relationship between opioid-related adverse outcomes and opioid dosages as well as differences in long-term postsurgical outcomes between patients who received different dosages of perioperative opioids or those who did and did not receive any opioids upon discharge. In the chronic setting, such research would evaluate associations between different magnitudes of change in opioid consumption and the participants' overall impression of improvement, side-effect burden, and function to identify clinically meaningful dosage reductions. This research could be performed prospectively by adding relevant assessments to clinical trials or observational studies that capture reductions in opioid consumption and retrospectively by conducting secondary analyses of studies that included opioid dosages and other informative variables. These analyses should consider demographic characteristics that might affect the determination of clinically meaningful reductions in opioid dosages.

7.3. Improving assessments of self-reported opioid-related adverse outcomes

Adverse outcomes that can be reported by participants can be assessed using active or passive methods. Active methods include asking participants about specific adverse outcomes or using a patient-reported outcome measure. Passive methods involve asking participants a general question at study visits regarding whether they are experiencing any new symptoms or problems since starting a trial or asking participants at the beginning of the trial to tell the investigators if they experience any adverse effects. Active methods can result in more frequent reporting of adverse outcomes but ensure that adverse outcomes of particular interest or importance are assessed. Another factor that could influence adverse outcomes reporting is how the assessment is introduced to participants. For example, some participants may be apprehensive that their opioids could be discontinued if they report adverse outcomes related to opioids. Language should be chosen carefully to explain the importance of accurate adverse outcome reporting to participants and to reassure them that adverse outcomes will not lead to medication discontinuation unless there is a risk to their safety. Future research evaluating and comparing active vs. passive methods to collect opioid-related adverse outcomes and different approaches to presenting such measures to patients has the potential to improve the reliability and validity of these important outcome assessments.

8. Conclusions

Development of novel pain management interventions that can decrease the use of opioid analgesics for treating acute and chronic pain is a major unmet public health need and an important research priority. The ability of such interventions to decrease the use of opioids without meaningful decreases in pain control or function is a critically important objective for future clinical trials. The considerations and recommendations presented in this article are intended to help guide the design, conduct, analysis, and interpretation of these trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Research design considerations for acute pain

Study objective	Primary outcome	Advantages	Challenges
1. Prevent use of opioids for acute pain	Opioid use (yes/no)	• Clinically meaningful – if patients never start opioids they will not misuse them or experience opioid-related adverse outcomes. • Short duration / little missing data.	• Could fail to identify an efficacious treatment by setting the bar for "treatment success" too high, especially in the case of major surgery or trauma.
2. Reduce opioid dosages for acute pain	Opioid dosage (measured via PCA or hospital records)	• Continuous opioid dosage generally has more power than dichotomous (i.e., yes/no). • Dose not require complete absence of opioid use for "success", thus potentially more relevant for major surgeries or trauma. • Short duration / little missing data.	• Little data available to determine clinical meaningfulness of different decreases in opioid dosages.
3. Reduce opioid-related adverse outcomes in acute pain	Adverse outcomes measured via passive or active data collection	• Arguably more clinically meaningful than decreasing opioid dosages. • Short duration / little missing data.	• Research is necessary to understand which adverse outcomes are most important for different populations and how to combine them into a single endpoint.
4. Eliminate the need for opioid prescription at hospital discharge for acute pain after surgery or trauma that would usually require one	Opioid prescription at discharge (yes/no)	• Clinically meaningful -- if patients do not go home with an opioid they are unlikely to become dependent. • Data recorded by research staff.	• Could fail to identify an efficacious treatment by setting the bar for "treatment success" too high, especially in the case of major surgery or trauma, although less so than for eliminating opioid use all together.
5. Decrease the duration of opioid use after surgery or acute pain problem	Duration of opioid use	• Continuous outcome that generally has more statistical power than dichotomous outcome. • No need to identify one specific time by which to eliminate opioid use.	• Little data available to select a clinically meaningful change in duration. • Longer follow-up provides more opportunity for missing data and requires more resources. • Measurement of at-home opioid use has more opportunity for error than opioid use measured in the hospital.
6. Reduce incidence of opioid use 3 months after surgery or acute pain problem in opioid-naïve patients.	Opioid use 3 months after acute pain problem	• Preventing longer-term opioid use is highly clinically meaningful. • For most surgeries or trauma, the physical tissue damage should be healed within 3 months, avoiding the problem of this outcome potentially being a "too high bar" like eliminating opioids altogether or leaving the hospital without opioids.	• With current opioid prescribing practices, few patients may be prescribed opioids 3 months after an acute pain problem, leading to relatively low power / large required sample sizes for this objective. • Measurement of at-home opioid use has more opportunity for error than opioid use measured in the hospital.

The population for these research objectives would include patients who have acute pain from recent surgery or trauma that would generally require opioid treatment. PCA patient controlled analgesia

Table 2.

Research design considerations for chronic pain

Study objective	Population	Primary outcome	Advantages	Challenges
1. Prevent initiation of opioid use for chronic pain	Chronic pain patients who have not taken opioids for a chronic pain condition and have failed non-opioid analgesics (i.e., lack efficacy or tolerability)	Use of rescue opioid medication or new opioid prescription for chronic pain (yes/no)	• Not initiating opioids is certainly clinically meaningful.	• If outcome is new opioid prescription: • Changing prescribing practices may limit the number of patients initiating opioids for chronic pain and thus this study may require a large sample size. • The variability in prescribing practices will create variability in the trial outcome. • Longer duration; greater opportunity for missing data.
2. Decrease opioid dosages in chronic pain patients	Chronic pain patients currently taking opioids	Daily opioid dosages	• Continuous opioid dosage generally has more power than dichotomous (e.g., yes/no). • Clinically meaningful to society to have fewer prescription opioids in circulation.	• Little data available to determine clinical meaningfulness of decreases in opioid dosages. • Accurate measurement of opioid dosages at home is more difficult than in the hospital, although various methods can improve accuracy. • Longer duration; greater opportunity for missing data.
3. Decrease opioid-related adverse outcomes in chronic pain patients	Chronic pain patients currently taking opioids	Opioid-related adverse outcomes	• Arguably more clinically meaningful to patients than a decrease in opioid dosages.	• Future research is needed to understand which adverse outcomes are most important for different populations and how to combine them into a single endpoint. • Longer duration; greater opportunity for missing data.
4. Prevent opioid misuse, use, OUD in chronic pain patients	Chronic pain patients currently taking opioids	Opioid misuse, use, or OUD	• Clinically meaningfulness of preventing opioid misuse, use, or OUD is indisputable.	• As with all prevention trials, will generally require larger sample sizes, especially if the incidence is relatively low. • Measurement of opioid misuse, use, and OUD may be challenging. • Longer duration; greater opportunity for missing data.

Table 3.

Future research priorities

	Proposed methodologies
Identification of patient priorities for opioid sparing	Structured interviews, focus groups, surveys in heterogeneous groups with varying ages, races, ethnicities, geographic locations, and pain problems or conditions who have used opioids for different amounts of times.
Identification of clinically meaningful reductions in opioid dosages	Associations between opioid dosage changes and overall impression of improvement, side effect burden, and function assessed prospectively or via secondary data analyses.
Evaluation of methods to assess opioid-related AEs	Prospective comparison of reliability and validity of active and passive adverse outcomes assessment methods with different methods of introducing the adverse outcome-related questions using diverse samples of patients taking opioids for different lengths of time.