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Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations

Jennifer S. Gewandter[a,*], **Robert H. Dworkin**[a], **Dennis C. Turk**[b], **John T. Farrar**[c], **Roger B. Fillingim**[d], **Ian Gilron**[e], **John D. Markman**[a], **Anne Louise Oaklander**[f], **Michael J. Polydefkis**[g], **Srinivasa N. Raja**[g], **James P. Robinson**[b], **Clifford J. Woolf**[f], **Dan Ziegler**[h], **Michael A. Ashburn**[c], **Laurie B. Burke**[i], **Penney Cowan**[j], **Steven Z. George**[d], **Veeraindar Goli**[k], **Ole X. Graff**[l], **Smriti Iyengar**[m], **Gary W. Jay**[n], **Joel Katz**[o], **Henrik Kehlet**[p], **Rachel A. Kitt**[a], **Ernest A. Kopecky**[q], **Richard Malamut**[r], **Michael P. McDermott**[a], **Pamela Palmer**[s], **Bob A. Rappaport**[t], **Christine Rauschkolb**[u], **Ilona Steigerwald**[v], **Jeffrey Tobias**[w], and **Gary A. Walco**[b]

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

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

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

[d]University of Florida, Gainesville, Fl, USA

[e]Queen's University, Kingston, Ontario, Canada

[f]Harvard University, Boston, MS, USA

[g]Johns Hopkins University, Baltimore, MD, USA

[h]German Diabetes Center at Heinrich Heine University, Düsseldorf, Germany

[i]Lora Group, LLC, Royal Oak, MD, USA

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

[k]Pfizer and Duke University, Raleigh-Duram, NC, USA

[l]GlaxoSmithKline, London,UK

[m]Eli Lilly. Indianapolis IN, USA

[n]Virtuous Pharma, Inc., Raleigh-Durham, NC, USA

[o]York University, Toronto, ON, CA

[p]Rigshospitalet, Copenhagen University, Denmark

[q]Endo Pharmaceuticals, Inc., Malvern, PA, USA

[r]Teva Pharmaceuticals, North Wales, PA, USA

[*]Corresponding author. *Address:* Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Box 604, Rochester, NY, 14642, USA. *Tel.:* +1 585 276-5661; fax: +1 585 244-7271. jennifer_gewandter@urmc.rochester.edu.

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The views expressed in this article are those of the authors, none of whom have financial conflicts of interest specifically related to the issues discussed in this article.

[s]AcelRx, Redwood City, CA, USA

[t]Arlington,VA, USA

[u]Johnson and Johnson, Titusville, NJ, USA

[v]Grünenthal GMbH, Aachen, Germany

[w]Jazz Pharmaceuticals, Palo Alto, CA, USA

Abstract

Although certain risk factors can identify individuals who are most likely to develop chronic pain, few interventions to prevent chronic pain have been identified. To facilitate the identification of preventive interventions, an IMMPACT meeting was convened to discuss research design considerations for clinical trials investigating the prevention of chronic pain. We present general design considerations for prevention trials in populations that are at relatively high risk for developing chronic pain. Specific design considerations included subject identification, timing and duration of treatment, outcomes, timing of assessment, and adjusting for risk factors in the analyses. We provide a detailed examination of 4 models of chronic pain prevention (i.e., chronic post-surgical pain, postherpetic neuralgia, chronic low back pain, and painful chemotherapy-induced peripheral neuropathy). The issues discussed can, in many instances, be extrapolated to other chronic pain conditions. These examples were selected because they are representative models of primary and secondary prevention, reflect persistent pain resulting from multiple insults (i.e., surgery, viral infection, injury, and toxic/noxious element exposure), and are chronically painful conditions that are treated with a range of interventions. Improvements in the design of chronic pain prevention trials could improve assay sensitivity and thus accelerate the identification of efficacious interventions. Such interventions would have the potential to reduce the prevalence of chronic pain in the population. Additionally, standardization of outcomes in prevention clinical trials will facilitate meta-analyses and systematic reviews and improve detection of preventive strategies emerging from clinical trials.

Keywords

Prevention trial design; Chronic post-surgical pain; Postherpetic neuralgia; Chronic low back pain; Chemotherapy-induced peripheral neuropathy; Risk factors

1. Introduction

Chronic pain is highly prevalent and difficult to treat [81]. Moreover, it is a costly public health problem, contributing to high health care costs and lost productivity [11,17,20,56,100]. Although certain risk factors can identify individuals who are most likely to develop chronic pain, very few interventions to prevent chronic pain have been identified, adopted for use in clinical practice, or approved by regulatory agencies. Chronic pain that develops after an injury has resolved, a toxicity or noxious element has been removed, or an infection has resolved have all been hypothesized, at least in part, to be mediated by nerve damage either from the insult itself or from an increase in the excitability and responsiveness of neurons in the spine (i.e., central sensitization) due to severe acute pain [179]. If nerve

damage during the initiating insult contributes to chronic pain, minimizing that damage as early as possible will likely decrease both acute and chronic pain. If the persistent pain is, at least in part, caused by central sensitization, preventing or minimizing acute pain at the time of insult may prevent the development of chronic pain. In other instances, such as chronic low back pain (CLBP), preventing re-injury could provide an approach for preventing chronic or recurrent pain.

In this article, we discuss research design considerations for clinical trials that evaluate both primary and secondary preventive interventions that target mechanisms that putatively contribute to the development of chronic pain. We focus on research design issues that can be applied to prevention trials for any chronic pain condition in which a patient population at high risk for developing chronic pain can be identified. We have selected 4 models of chronic pain prevention to discuss in detail: chronic post-surgical pain (CPSP), postherpetic neuralgia (PHN), CLBP, and chemotherapy-induced peripheral neuropathy (CIPN). Since estimates of pain prevalence vary greatly depending on how the data are collected, it is difficult to determine which pain conditions have the greatest personal and public health impact. Thus, these four examples were chosen because they (1) represent models that could be amenable to primary or secondary prevention; (2) are conditions that are treated with a range of modalities including pharmacological, invasive, and non-pharmacological / non-invasive interventions; and (3) represent pain induced by multiple etiologies. Specifically, we chose models of surgical trauma, viral infection, injury, and a toxicant, as these models are most commonly discussed in the context of preventing chronic pain. This article is not a systematic review of all published chronic pain prevention studies in these 4 fields and will not comment on efficacy of any given preventive treatment based on single studies.

2. Methods

An Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) meeting, including a diverse group of participants from universities, government agencies, industry, and a patient advocacy group, with 25 representatives from the United States, 2 from Canada, and 4 from Europe, was held to discuss research design considerations for chronic pain prevention trials. Participants were selected to represent a broad range of relevant topics, areas of expertise, and disciplines, while the number of participants was limited to promote productive and efficient discussion.

To facilitate discussion, background lectures were presented that examined (1) neurobiologic aspects of preventing acute and chronic pain (CJW); (2) risk factors for the development of chronic pain, including genetic predisposition (RBF); (3) research design considerations for clinical trials of perioperative analgesic medications to optimize acute postoperative pain management and recovery (SNR); (4) chronic post-surgical pain (IG); (5) postherpetic neuralgia (RHD); (6) painful diabetic peripheral neuropathy (DZ); (7) HIV and chemotherapy-associated peripheral neuropathies (MJP); (8) complex regional pain syndrome (CRPS) type 1 (ALO); (9) chronic neuropathic low back pain (LBP) (JDM); (10) chronic musculoskeletal LBP (JPR); and (11) critical methodologic aspects of clinical trials to prevent chronic pain (JF).

To supplement the background presentations, a review was performed for each of the prevention models discussed here to identify any recent randomized clinical trials (RCTs) with relevant prevention design features that could be described as examples of the recommendations that were formulated through the meeting and subsequent discussions. PubMed was searched for articles published between June 2009 and December 2014 using the search strategies outlined in Appendix 1.

Ideally, recommendations for clinical trial designs should be based on systematic studies; however, because relatively few randomized clinical trials investigating preventive interventions for chronic pain have been conducted (e.g., see Chaparro et al. [30] and Han et al. [68]), information that would make it possible to attempt to attribute falsely negative trial results to methodological issues is lacking. The design recommendations presented in this article are based primarily on existing literature along with the experience and expertise of the authors, the background presentations, the discussions that subsequently occurred during the meeting, circulation of a draft manuscript to all authors, and iterative revision of the draft manuscript until approval of all authors for submission for publication was achieved. We focus on design considerations that are particularly relevant to prevention trials. Previous IMMPACT recommendations as well as the CONSORT statement and comprehensive text books are available for guidance on more general methodological issues of clinical trials (e.g., randomization procedures, choice of active vs. inactive placebo) [49,62,145,149]. Figure 1 presents a general research design schema for chronic pain prevention trials that provides a framework for many of the specific considerations discussed below. We believe that implementation of these recommendations in future chronic pain prevention trials would expedite the development of effective prevention strategies and facilitate the preparation of more informative systematic reviews and meta-analyses.

3. General considerations

3.1. Acute pain severity

One prominent hypothesis regarding mechanisms underlying the development of chronic pain is that nociceptive processes, which also cause acute pain, can cause peripheral or central sensitization, leading to the initiation and maintenance of chronic pain [90,110,180]. Thus, one investigational approach has been aimed at reducing acute pain during or shortly after an inciting painful insult in order to reduce both acute pain and the potential development of chronic pain [5, 30]. Monitoring acute pain intensity allows one to test the hypothesis that the effect of treatment on preventing chronic pain is mediated by its effect on acute pain. For example, if the preventive analgesia does not decrease either acute pain or chronic pain, further efforts to decrease acute pain with other agents or different dosages of the same agent as a method to prevent chronic pain would be warranted. If acute pain severity is lower in the treated group than in the placebo group, but no difference in chronic pain is found between groups, decreasing acute pain may not be sufficient to prevent chronic pain, a possibility that has been discussed by Katz and Seltzer [91]. Alternatively, it is possible that the threshold of acute pain that triggers central sensitization is even lower than the level experienced by the treated group. When deciding whether to further pursue preventive treatments that target acute pain levels, investigators should consider the degree to

which the acute pain was decreased in the treatment group and whether a larger decrease in acute pain to reach a possibly lower acute pain threshold is a realistic goal. For trials that use prevalence of any chronic pain as the primary outcome, an acute pain severity measure that assesses a similar type of pain as in the chronic pain outcome (e.g., burning pain, pain on movement) should be used.

3.2. Outcome measures

Previous IMMPACT recommendations suggested including pain intensity and physical and emotional functioning as core outcome domains in chronic pain trials [162]. Our recommendations emphasize pain outcomes, including presence and severity, to illustrate various methodological issues in the prevention setting. However, these considerations are also generally applicable to other outcomes that can be important to include in prevention trials, including physical and emotional functioning and sleep, which we also discuss when their assessment is particularly important. When assessing pain severity it is important to consider the time frame (e.g., a single time point after randomization or a combination of multiple assessments). Presence outcomes include any pain versus no pain or pain above or below a “clinically meaningful” or moderate pain intensity level (e.g., average pain intensity of 3 out of 10 or greater). Although an analysis based on “clinically meaningful” pain levels may have a higher impact from a clinical and public health perspective, it may also have less power because the incidence of moderate to severe pain will be lower than the incidence of any pain. Furthermore, it may be difficult to identify clinically meaningful levels of pain for the different chronic pain conditions given that there has been little systematic examination of patient-reported assessments of the long-term impact of different levels of pain. Future studies should investigate patient opinions regarding the minimal pain intensity and duration that would be considered to be clinically meaningful in relation to the probability of developing such chronic pain as well as risks and costs of the potential preventive treatment (e.g., what level and nature of side effects would the patient be willing to tolerate for an intervention that reduced the probability of a certain intensity of pain in the future by a specified amount or time period). Better understanding of how to define the minimal threshold of chronic pain that would be considered clinically meaningful will allow researchers to more accurately determine the necessary sample sizes for RCTs of preventive analgesic treatments. It is important to note that such clinically meaningful differences should only be used to define responders at the individual level, and should not be extrapolated to a required minimum difference between groups in pain intensity [47]. Issues regarding outcome measurement and timing in specific prevention models are discussed further below.

Post-randomization initiation of non-study pain medications can complicate the interpretation of pain severity ratings. Initiation of such pain medications is likely to be more common in prevention trials than in treatment trials in which patients have been in pain for several months or more and often are already taking pain medications at stable dosages. Because prevention trials start prior to or soon after pain onset, it is generally not possible to require that patients use only those non-study pain medications they were taking regularly before the initiation of the trial. Therefore, innovative ways to manage post-randomization initiation of non-study pain medications in the analyses are especially important in

prevention trials. As a potential solution to this problem, the U.S. Food and Drug Administration (FDA) [166] recently recommended including an outcome that would jointly assess pain and rescue medication in analgesic trials. For example, a responder analysis could be conducted in which participants are considered responders if they report chronic pain less than a pre-specified value and take less than a pre-specified amount of rescue medication. The reliability and responsiveness of such a composite outcome measure has yet to be established and therefore this approach cannot be suggested for primary outcome measures. However, considering that there is no existing evidence-based solution for this problem, and that these types of measures have face validity, we recommend that investigators consider including some type of composite measure as a secondary outcome. The inclusion of such measures in future trials will provide data to examine the reliability, responsiveness, and validity of such approaches. Another option for prevention trials is an analysis comparing treatment groups with respect to the presence or absence of pain of any level of intensity at a pre-specified extended, post-insult time point (i.e., at time point when the pain is considered to be chronic). This analysis would likely not be complicated by the use of rescue or concomitant analgesic medication because it is rare that chronic pain is completely eliminated by medication.

3.3. Challenges of evaluating assay sensitivity

One challenge of conducting chronic pain prevention studies is that very few, if any, hypothesized interventions have shown replicated evidence of efficacy; therefore, active comparators are not readily available to assess the assay sensitivity of particular outcome measures or trial designs. Once an efficacious preventive intervention is identified for a condition, the sensitivity of the outcomes proposed in this review can more easily be evaluated. Another challenge occurs when pain existing prior to the insult cannot easily be distinguished from the pain subsequently caused by the insult. For example, patients who have burning pain in the feet from diabetic peripheral neuropathy (DPN) are likely to find it impossible to distinguish this pain from burning pain in the feet from CIPN. Additionally, patients undergoing surgery for back pain may not be able to distinguish between chronic pain caused by the surgery and residual unresolved back pain. In these instances, it may be advantageous to exclude such patients from prevention studies. In contrast, patients with burning pain in the feet from DPN can probably distinguish their DPN pain from new onset thoracic PHN pain. In such cases, patients with existing pain can be included in the trials, but existing chronic pain should be examined in the analyses in a similar manner to risk factors described in Section 3.4.

3.4. Pre-specified adjustment or stratification for risk factors

Adjustment for a limited number of well-established risk factors for the development of chronic pain could increase the ability to detect a preventive effect [86,166]. In order to control type I error, any covariate adjustment made in the primary analysis or secondary analyses should be specified before the treatment assignments are revealed. Data from such pre-specified analyses could also be used as further evidence to address the validity of the proposed risk factors. However, it is important to note that cohorts participating in a clinical trial may be quite different from the target population, and therefore associations found using clinical trial data may not necessarily reflect the associations that exist in the

population. Furthermore, including interactions between treatment and potential risk factors for the development of chronic pain can identify possible sub-groups for which a preventive intervention is more likely to be efficacious. Such findings would generally be considered to be hypothesis generating, unless incorporated in the primary analysis through pre-planned adjustment for multiplicity. Researchers should also consider using well-established risk factors as stratification variables in randomization plans.

A potential alternative to adjustment for chronic pain risk factors is to consider risk factors in the study entry criteria to increase the incidence of chronic pain in the sample population. This is a common practice in PHN prevention trials that often include only herpes zoster patients older than 50 years of age. CIPN prevention trials always enroll patients receiving chemotherapy treatments with the highest risk of CIPN, including taxanes, platinum agents, and vinca alkaloids. In other conditions in which risk factors for chronic pain have less evidential support, this may not be appropriate. However, greater acute pain intensity (i.e., severity) has frequently been found to increase the risk of chronic pain and should therefore be considered as a possible inclusion criterion or covariate in secondary prevention trials of chronic pain. The extent to which more restrictive eligibility criteria would hinder recruitment rates should be considered before their implementation. Furthermore, such eligibility criteria would decrease the generalizability of the findings to only those patients who are identified as high risk for the development of chronic pain. On the other hand, a trial that includes only those patients considered to be at high risk will likely require a smaller sample size.

In general, the number of adjustments made in the primary analysis should be limited, because covariates that are not predictive of the outcome can decrease power, especially for studies with a small number of participants. It is also important to note that it is generally not appropriate to adjust for a risk factor that is measured post-baseline because it could be altered by the experimental treatment. For example, adjusting for cumulative dosage of chemotherapy in a trial of a preventive treatment for CIPN might produce misleading results because the treatment may have an effect on both the cumulative dosage of chemotherapy and the development of CIPN. An exception to this occurs when one is interested in testing specific hypotheses concerning factors that may mediate the effect of a treatment on prevention of pain. For example, structural equation models [117,135] can be used to examine whether the effect of a treatment on prevention of chronic pain is mediated through its effect on acute pain. It is beyond the scope of this work to perform a systematic review of the literature to identify and evaluate the level of evidence for risk factors for each of the 4 chronic pain models discussed here. However, investigators should review the literature when planning chronic pain prevention trials to identify evidence-based risk factors that should be considered when developing the study design and analyses.

3.5. Genetic Factors

Genetic factors contribute significantly to the variability in both pain and analgesic responses; therefore, consideration of genetics is important in the design and conduct of chronic pain prevention trials. Multiple candidate genes have been associated with laboratory measures of pain sensitivity and with clinical pain [38,39]. In particular, three

genes have shown consistent associations with both experimental and clinical pain responses: the catechol-O-methyl transferase gene (*COMT*), the mu-opioid receptor gene (*OPRM1*), and the GTP-cyclohydrolase gene (*GCH1*) [115]. Regarding *COMT*, polymorphisms and haplotypes have been associated with laboratory pain sensitivity, and acute and chronic clinical pain [13,40], including long-term outcomes after back surgery [143]. Similarly, the A118G polymorphism of *OPRM1* has been associated with experimental pain sensitivity and with clinical pain [53,71,123], including long-term outcomes of acute back pain [124]. Finally, *GCH1* genotypes have been associated with experimental and clinical pain responses across several cohorts [15,28,159,160], and GCH1 genotypes have predicted outcomes from lumbar spine surgery [96,160]. Genetic factors can also impact postoperative analgesic responses, which may impact CPSP since acute pain severity is among the strongest predictors of CPSP. In addition to multiple genes that impact drug metabolism [144], *COMT* [29,36] and *OPRM1* [80,152] have been associated with postoperative opioid analgesic requirements.

Importantly, these genes can interact with each other and with non-genetic factors to influence pain responses and analgesic requirements. For example, previous studies have reported that *COMT, OPRM1*, and *GCH1* show sex-specific associations with pain responses [14,15,124]. In addition, *COMT* haplotypes have been shown to interact with psychological functioning (i.e., pain catastrophizing) to predict both experimental and clinical shoulder pain outcomes [58,60]. Research has shown that *OPRM1* and *COMT* exerted combined effects on the total dosage of morphine consumed by patients with chronic cancer-related pain [138]. Specifically, individuals who were homozygous for both the Val allele of *COMT* Val158Met polymorphism and the 118A allele of *OPRM1* required significantly lower morphine dosages compared to all other groups. Genetic factors can also directly impact responses to pharmacologic interventions; therefore, genetic variables should be considered for incorporation into trials designed to reduce the risk of chronic pain as potential covariates to increase power or allow examination of differential treatment response in patient subgroups.

Although some trials may be developed to address genetic factors, many trials may not be designed or have sufficient power to test genetic hypotheses. In these cases, collection and storage of biological samples for future genotyping would be an ideal approach. This practice could create a rich resource for future analyses designed to identify genetic influences on the development of chronic postoperative pain and its prevention. The added logistical and administrative burden is relatively small in proportion to the potential scientific and translational value that such information could provide.

4. Design considerations in the context of 4 illustrative prevention models

4.1. Chronic post-surgical pain (CPSP)

Several definitions of CPSP have been proposed, including a recent proposal based on research findings and current knowledge of pathophysiologic mechanisms [172]. CPSP occurs after the damaged tissue has healed and thus a large component is thought to be neuropathic [70]. Although CPSP is generally thought to be a result of surgery-induced nerve damage, the exact mechanisms are unknown and whether the mechanisms are similar

between different surgery types is also unknown. Potential causes include peripheral and central sensitization [21,105,110,179,180]. It is important to note that in specific circumstances, pain is likely not neuropathic. For example, postherniotomy pain could be due to irritation from the mesh and once that mesh is removed the pain could subside. CPSP has been considered an excellent model to study chronic pain prevention because the exact timing of the injury is known, allowing for primary prevention. One potential drawback of CPSP models is that surgery is often used to treat painful conditions and it can be difficult to avoid confounding from pre-surgery pain in the outcome analyses. CPSP models with little to no pre-surgical pain (e.g., thoracotomy) can be used to prevent confounding.

Preventive efficacy of a compound for CPSP should first be studied in surgical pain models with higher incidences of CPSP (i.e., 20%-60%), such as mastectomy, thoracotomy, amputation, and inguinal hernia repair [21,70] to decrease necessary sample sizes. Pain prevention studies using similar pharmaceutical agents in different post-operative models have had inconsistent results [27,120,121,150], suggesting that different mechanisms may be involved compared to other persistent postoperative pain states. This inconsistency could be due to variable efficacy of similar drugs in different models, or could represent false negative results due to low power or other methodological issues. Therefore, any interventions found to be efficacious in surgeries with high rates of CPSP should be tested in other models before being used clinically in other surgical settings [89,99].

4.1.1. Treatment timing—Primary chronic pain prevention, which is treatment initiated before exposure to the pain causing agent or event, is ideal. Primary preventive treatments for CPSP should generally be initiated so that treatments are ideally at their effective dosage before the surgery begins. This may require days or even weeks of titration to target dosage with such medications as duloxetine, gabapentin, or pregabalin. Many prevention studies for CPSP have initiated gabapentin and other oral medications between 1 hour and 1 day prior to surgery [3,12,24,25,27,33,51,52,57,66,95,97,98,101,108,116,131,133,147,148,165]. One study initiated treatment with an antidepressant 2-3 weeks prior to coronary artery bypass surgery; however, chronic pain was only assessed as part of a composite quality of life measure [31].

Acute post-surgical pain includes all pain that occurs before healing of the tissue damage from the surgery [106]. When feasible and reasonable, preventive interventions for CPSP should generally be continued as long as the tissue damage from the surgery is present and for the entire duration of acute post-operative pain. This type of pain, however, can last for months for certain surgeries (e.g., thoracotomy or total knee replacement). Depending on the type of investigational intervention, it may not be feasible or sensible to extend the treatment for the full duration of the acute pain period. For example, an intravenous (IV) or subcutaneous analgesic that is given throughout the surgery and / or post-operative stay will likely not cover the entire duration of the acute pain period, but may still be effective at reducing chronic pain. Several prevention trials have investigated IV or subcutaneous medications administered before, during, and between 1 and 4 days after surgery [34,42,65,72,158,171]. An oral analgesic, however, can be administered throughout the entire acute pain period, in both clinical trials and in clinical practice, thus continuing such an intervention throughout the entire acute pain recovery period should be considered. This

recommendation is based on the hypothesis that chronic pain is caused, at least in part, by pathophysiologic mechanisms associated with acute pain. If another mechanism (e.g., nerve injury) is responsible for the development of CPSP, analgesic treatment for the entire duration of tissue damage may not be necessary, especially in instances where continued treatment with the experimental intervention is associated with unacceptable adverse events or high cost. We suggest that the time period in which post-surgical pain is considered acute should be based on natural history data specific to each surgery model or, in the absence of epidemiological data, the clinical expertise of the investigator. Several clinical trials have extended the investigational treatment between 5 and 14 days post-surgery [3,27,51,52,67,66,95,108,120,133].

4.1.2. Outcome measures and assessment timing—Whether using a continuous pain intensity measure (e.g., numeric rating scale (NRS) or visual analog scale) or a binary any pain vs. no pain measure, “pain intensity upon movement” should be included in CPSP trials as a component of the acute and chronic pain assessments [93]. Various trials have assessed CPSP with less specific movement, for instance “while coughing” [125,165], “during daily activities” [12], “while moving” [88,170] or during a defined movement protocol [3]. Procedure-specific validated assessments of pain-related functional consequences, such as those described for hernia surgery [54], thoracic surgery [140], and breast [4] surgery, have been developed. Inclusion of these measures in future studies could help characterize their responsivity to change, which has yet to be investigated. Pain measures that assess both neuropathic and non-neuropathic pain qualities such as the Short-form McGill Pain Questionnaire-2 [50], or that only assess neuropathic pain qualities such as the Neuropathic Pain Symptom Inventory [22], can also be included to assess the nature of the CPSP [106]. If the pain qualities are different before and after surgery, the pain can more confidently be attributed to the surgery. Multiple studies have included neuropathic pain measures as CPSP study outcomes [12,19,27,33,51,65,67,78,88,108].

The primary assessment time for CPSP should be assessed at a point after surgery when the tissue damage would be expected to have healed, but not so long that the prevalence of the CPSP is too low to detect a difference between groups with a reasonable number of study subjects. Early CPSP assessments should be administered shortly after the surgical tissue damage is expected to heal. In order to improve opportunities for future meta-analyses, all CPSP trials should also include 3, 6, and 12 month assessments, whenever possible. Acute pain outcomes (e.g., 24 - 48 hours post-surgery) and use of non-study analgesic treatments should be collected even though the primary aim of the study is to investigate the prevention of CPSP. These data can contribute to our understanding of whether acute pain predicts chronic pain and whether different acute factors contribute to the transition from acute to chronic pain (i.e., 24 – 72 hours to 3 months) than those that contribute to the persistence of chronic pain (i.e., 6 months to 1 year), which has been investigated in previous studies [87,146].

4.2. Postherpetic neuralgia (PHN)

PHN is persistent pain that occurs following herpes zoster (HZ) infection (i.e., shingles), which may be caused by central sensitization from acute HZ pain [142]. HZ causes a

unilateral, dermatomal, usually painful, vesicular rash [45]. The 3 best-established risk factors for PHN after HZ infection are advanced age (> 50 years), greater HZ rash severity, and more severe pain during the HZ infection [46]. Approximately 20% of patients who have HZ and are over age 50 develop PHN even with antiviral therapy, which is the only preventive treatment for PHN that has shown replicated efficacy [18,44,83,163,164,178]. We recommend that investigators include only patients over 50 years of age in these studies to maximize power. Furthermore, they should consider using a minimum acute pain score (e.g., greater than 3 on a 0-10 NRS) at the time of enrollment to further increase the number of patients who will develop PHN [32,85,111,118,175].

A vaccine is available that decreases the risk of HZ infection and in so doing decreases the risk of developing PHN. However, the vaccine did not decrease the risk of developing PHN in those patients who developed HZ after being vaccinated [127] and is therefore less directly relevant to the prevention of chronic pain.

4.2.1. Treatment timing—Prior to the HZ infection, it is difficult to predict which individuals will develop PHN therefore, only secondary prevention (i.e., prevention of transition to chronic pain after exposure to a pain causing agent or event) is possible without recruiting an extremely large sample of participants. Ideally, preventive treatment should be started as soon as possible after the initial insult, in this case the HZ infection and rash onset. Patient recruitment is often a limiting factor in how early in the course of HZ progression the preventive treatment can be initiated. Patients typically do not visit their doctor until after the rash appears and HZ is usually treated by primary care physicians. Thus, close collaborations with primary care physicians are encouraged [126]. Investigators should also identify a maximum duration of HZ rash for study eligibility. Cut-offs of 3 [174,178], 6 [43] or 7 days [84,130,168] following rash onset have been used in previous trials. Because antiviral treatment decreases HZ severity and the duration of PHN [163], all subjects in PHN prevention trials should be treated with an antiviral agent in addition to either the investigational treatment or placebo.

The natural history of HZ infection and progression of PHN has been studied in detail [6,45]. Pain existing up to 30 days after HZ rash onset is considered acute and preventive treatment throughout this time period in clinical trials is encouraged. This could include oral medications taken daily for up to 30 days (but probably for not less than 2 weeks) as well as single or intermittent treatments whose effects are thought to persist beyond their administration (e.g., nerve blocks of various types). Investigation of treatments that target the infection (e.g., novel antiviral therapies or treatments that enhance immune function) is an exception to these considerations. These treatments would likely only be beneficial while the HZ infection is active, although their effects on reducing nerve damage could have long-term benefits. Seven days of antiviral treatment was shown to decrease the duration of PHN in a study in which the median time to last positive viral culture was 2 days in the placebo group; this suggests that 7 days likely covers the period of active infection in the majority of patients and would be a reasonable treatment time for interventions that target the acute infection [163].

4.2.2. Outcome measures and assessment timing—The frequency with which PHN eventually resolves depends on how long after rash onset the HZ-associated pain has persisted. The rate of pain resolution in patients whose pain has persisted at least 4 months after rash onset appears to be less than the rate of resolution in patients whose pain has lasted less than 4 months; thus, it has been suggested that PHN can be defined as pain persisting at least 4 months after rash onset [45]. This 4 month time point can be considered for primary analyses in PHN prevention trials, although pain persisting for 90 days after rash onset – the definition of PHN used in the Shingles Prevention Study of vaccination – is also reasonable [127].

Prevalence of any persisting HZ-associated pain at a pre-specified time point after rash-onset has been used to assess efficacy of PHN prevention treatments [23,84,107,130,168]. Whether using a continuous pain intensity measure or a binary pain prevalence outcome measure, participants in PHN prevention studies should be instructed to only consider the pain that is located in the area that their HZ rash had been present. If overall pain intensity is assessed using a NRS or other rating scale, participants should also be asked separately about pain in response to non-painful stimuli, especially from light touch (i.e., allodynia).

4.3. Chronic low back pain (CLBP)

CLBP was recently defined by the NIH task force on research standards for CLBP as pain occurring between the lower posterior region of the rib cage and the horizontal gluteal fold that has lasted every day for at least 3 months and occurred on at least half the days for a minimum of 6 months [37]. A recent global evaluation of disease burden found that LBP was the greatest contributor to disability of the 291 diseases studied [79]. The strongest predictor of developing CLBP is experiencing an acute LBP episode. Studies suggest that only 25% to 58% of patients with acute LBP will fully recover within 12 months of the original episode, with the remaining patients experiencing recurring episodes of acute pain or persistent chronic pain [35,76,94,132]. Predicting which acute back pain patients will develop chronic pain is challenging, which can make it difficult to identify patients to enroll in a prevention trial.

The STarT Back Tool (SBT) combines 9 repeatedly identified risk factors (i.e., leg pain, comorbid pain, 2 disability items, bothersomeness, catastrophizing, fear, anxiety, and depression). Considering that multiple studies demonstrate the ability of the SBT to predict chronic pain or disability [16,77,169], investigators could consider including this as a covariate in the primary analyses of prevention trials. This practice would also better characterize the prognostic value of the SBT for different populations of acute back pain patients. The SBT was shown to have relatively high specificity when predicting poor outcomes in 2 studies [77,169]; therefore, investigators could consider using the SBT to identify patients likely to experience CLBP for enrollment in prevention trials. However, because of the relatively low sensitivity of the SBT, even in the studies demonstrating its prognostic value, many patients who would be excluded from a clinical trial using this measure would develop CLBP, potentially limiting the generalizability of the trial's results. It is important to note, however, that the optimal balance between sensitivity and specificity of a screening tool depends on the purpose of the screening [119].

Optimal participants for a CLBP prevention trial would be patients who are experiencing their first LBP episode; however, these patients are relatively rare in the adult population and such an inclusion criterion could be expected to increase the enrollment time and cost of a trial. In order to minimize the number of patients included in a prevention trial who already frequently experience recurrent LBP episodes, investigators could consider limiting recruitment to patients who have not visited a clinician for LBP or experienced a recurrence of back pain for some period of time before the current episode, for example, 6 months or 1 year [169].

The pathophysiological mechanisms of nonspecific LBP are largely unknown. Like the other chronic pain conditions discussed here, severe acute LBP has been shown to predict CLBP. Thus, controlling acute LBP initially could potentially prevent chronic back pain by decreasing central sensitization or other peripheral or central mechanisms. However, evidence suggests that CLBP also has a large psychosocial component. Furthermore, physical therapy and spinal manipulation are often used to promote healing of acute LBP in clinical practice. As a result, the types of interventions used to prevent CLBP often include non-pharmacologic treatments. The type and mechanism of an intervention intended to prevent the development of CLBP in patients with acute back pain must be carefully considered when applying these recommendations to trials designed to test these interventions.

4.3.1. Treatment timing—The CLBP study designs proposed are trials of secondary prevention and thus the acceptable length of time after initiation of the acute pain episode needs to be considered. Assuming that decreasing acute LBP truly prevents the transition to CLBP, enrolling participants as close as possible to the start of their pain episode would be optimal. Data from a prospective study by Croft et al. [35] suggest that the earlier patients present at the clinic for treatment, the more likely they are to recover by 3 and 6 months. Previous prospective studies have recruited LBP patients experiencing a LBP episode of less than 2 [73], 3 [55,153], and 6 weeks [176].

The exact time point at which an acute back pain injury begins and is resolved is difficult to identify and likely differs greatly among patients. Research suggests that few patients who still experience LBP at 3 months after the initial episode will fully recover [26,35,82,94,132], suggesting that by 3 months acute LBP has likely become chronic, which is consistent with the NIH task force definition of CLBP [37]. Thus, administering preventive treatments for 3 months after enrollment would likely be sufficient to cover the time period of most patients' acute injury pain. A full 3-month treatment may not be necessary, however, for interventions with lasting effects such as self-hypnosis or relaxation training. The duration of the preventive interventions should be based on previous studies of similar interventions in order to avoid unnecessary burden on patients and reduce study costs.

4.3.2. Outcome measures and assessment timing—The NIH task force recommends that all research studies involving participants with LBP should include a minimum dataset with the domains of physical function, depression, sleep disturbance, and catastrophizing [37]. The presentation of CLBP is variable; patients can experience a

consistent level of pain or recurring episodes of severe pain interspersed with periods of moderate pain intensity or even no symptoms [94]. This variable pattern can make it difficult to capture the pain experience for all patients in a single primary endpoint if the intervention is targeted at preventing both steady chronic and episodic pain. CLBP prevention studies have used outcomes such as pain intensity (with various recall periods) at a pre-specified time point [2,59,61,109,157,161,173]. Although these outcomes can provide valuable information, if an individual experiences variable pain, the outcome will be very different depending on whether the pre-specified assessment point falls during a period of high or low pain [119]. Similarly, a time to recovery outcome (used in [69]), may not reflect severity for episodic pain patients. A recent study by Williams et al. [176] used a time to recovery of *at least* 7 days, which could increase the validity of this type of outcome measure for episodic patients whose pain fluctuates frequently. The number of low back pain recurrences or painful months in a pre-specified time period (used in [41,103]) will more accurately represent episodic or variable pain. These outcomes, however, may minimize the pain experience of an individual who consistently experiences moderate to severe pain. By monitoring back pain on a daily basis, from baseline until 6 months, patients could be stratified into 2 groups: those that meet the NIH task force definition of CLBP (i.e., pain every day for 3 months or for half of the days for 6 months) and those that do not. This type of outcome measure would include both chronic and frequent episodic pain, but would have limited power due to its dichotomous nature and the fact that it does not account for pain severity. The area under the curve (AUC) of periodic pain intensity assessments over a pre-specified period of time would represent pain severity in individuals who experience different pain patterns and would be a continuous outcome variable, thus potentially increasing the power of the analysis. This type of outcome variable was used in the Shingles Prevention Study to characterize the overall severity and persistence of HZ pain [127]. The frequency of assessment for an AUC outcome should be determined based on consideration of patient burden and reasonable recall periods. Suni et al. [157] required patients to keep a weekly diary for 12 months, suggesting that frequent data collection is possible; however, the level of diary compliance was not reported.

Investigators should consider assessing the efficacy of CLBP preventive treatments at 3, 6, and 12 months or a period that encompasses these time points. These time points are consistent with the NIH task force [37] definition of CLBP as well as with the many epidemiologic studies that investigate persistent CLBP at 12 months. Study designs should avoid assessing the outcome too close to the end of the preventive intervention in order to clearly distinguish prevention as opposed to management of symptoms. For example, if the investigational treatment lasts for 3 months, investigators should consider measuring the primary outcome variable at 6 or 12 months.

4.4. Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is caused by various neurotoxic chemotherapy agents (e.g., platinum agents, taxanes, vinca alkaloids, bortezomib) and includes sensory symptoms ranging from numbness and tingling to pain and allodynia [7, 10]. Few clinical studies have investigated chronic CIPN, or CIPN that persists after completion of chemotherapy. The estimated prevalence of chronic CIPN symptoms persisting 5-15 years after completion of treatment with platinum agents

ranges from 13%-35% [64,156]. One study found that 32% of patients taking vincristine still reported neuropathy symptoms after completing vincristine therapy, with a median duration of follow-up of 34 months; however, no patients who were 40 months post-treatment reported neuropathy symptoms [134]. Ten percent of patients who received bortezomib developed ≥ 2 grade neuropathy that persisted for at least 1 year [139]. However, none of these studies investigated rates of persistent *painful* neuropathy, specifically. One study showed that 18% of patients receiving paclitaxel for breast cancer reported neuropathic pain after an average of 9 years and that patients who had experienced CIPN during chemotherapy were 3 times more likely to report neuropathic pain after chemotherapy completion [137]. However, they also found that diabetes and osteoarthritis were associated with neuropathic pain in these cancer survivors [137].

Many previous studies that examined preventive treatments for CIPN investigated prevention of continually occurring acute symptoms present during ongoing chemotherapy administration and did not investigate prevention as it is classically defined (i.e., assessing outcomes after the preventive treatment is terminated) [74]. Therefore, although these trials are different from treatment trials because the investigational treatments are started either prior to or at the same time as chemotherapy with the goal of preventing neuropathy symptoms, we will not discuss these designs in this article.

Eligible patients for CIPN prevention trials should be patients scheduled to receive a neurotoxic chemotherapy (e.g., platinum agents, taxanes, vinca alkaloids, bortezomib). Patients should also have a life expectancy that is at least 6-12 months longer than their scheduled course of chemotherapy to minimize trial attrition. Investigators should consider excluding patients who have diabetes, HIV, or alcoholism, all of which can also cause a peripheral neuropathy. Inclusion of these patients in trials can make it difficult to determine whether CIPN, a neuropathy from another cause, or the combination of multiple types of neuropathy is being investigated in the trial. Patients with diabetes have been excluded from previous CIPN prevention studies [75,141].

The specific pathophysiological mechanism of nerve damage associated with CIPN varies depending on the neurotoxic agent [7], but acute nerve damage at the time of infusion may transition into sub-acute and chronic pain, and it is possible that minimizing acute pain may limit this transition. It is also possible, however, that minimizing acute pain will allow patients to receive a higher cumulative dosage of chemotherapy, which could actually lead to increased severity of chronic painful CIPN. Other interventions could target putative mechanisms of nerve damage, such as oxidative stress. Clinical trial designs for CIPN prevention should be tailored based on the treatments' proposed mechanism(s) of action.

4.4.1. Treatment timing—Primary prevention can be studied in CIPN by initiating the investigational treatment on or before the first day of chemotherapy. Although achieving the target dosage of the investigational medication before chemotherapy is administered would be ideal, this may not be feasible if, for example, chemotherapy must be administered very soon after a cancer diagnosis and the medication must be titrated slowly to the effective dosage, such as would likely be true of anti-epileptics. In certain cases, investigators may choose to investigate secondary prevention of painful CIPN by enrolling patients who

develop early CIPN symptoms such as numbness and tingling after the initiation of chemotherapy. Doing so would increase the percentage of participants who will develop chronic painful CIPN in the sample, but such timing could also attenuate the beneficial effects of a truly preventive treatment that requires very early administration to prevent nerve damage.

It would generally be recommended that preventive treatments should be administered throughout the duration of the insult that causes chronic pain; however, CIPN is unique in that the pain-inducing insult occurs at multiple intervals over a period of time that often lasts for months [10,122,136,177]. Whether the treatment would likely be best given throughout the full duration of the prescribed chemotherapy or only proximal to each chemotherapy infusion depends on the proposed mechanism and mode of administration of the investigational drug. For example, a bolus intravenous dose of an anti-inflammatory or other agent hypothesized to prevent nerve damage may be best administered directly before or after each chemotherapy infusion as was performed in multiple studies [102,104,113,141,155]. In fact, daily infusions of an investigational prophylactic CIPN treatment throughout the full course of chemotherapy are not likely to be feasible. On the contrary, oral or topical medications that target the nervous system – such as anti-epileptics, anti-depressants, or anti-inflammatory agents that are being used to decrease pain or augment pain inhibition – would likely best be initiated before the start of chemotherapy and continued until the end of chemotherapy (e.g., [1,75,92]) or for 2 weeks to 3 months after chemotherapy completion (e.g., [8,9,63,128,129]).

4.4.2. Outcome measures and assessment timing—As with the other prevention models, possible outcome measures include the intensity or incidence of any pain or minimal pain intensity associated with chemotherapy at a pre-specified time following cessation of chemotherapy. Previous studies of CIPN prevention, have focused on composite, and sometimes crude, measures of neuropathy symptoms, such as the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) and European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire- Chemotherapy-induced Peripheral Neuropathy-20 (EORTC-QLQ-CIPN20) scales and not pain specifically [74]. This could explain why trials of gabapentin and amitriptyline, which are known to work for other neuropathic pain conditions, have failed to detect a preventive treatment effect in CIPN [92,114] and why many other trials have also failed [74]. A recent CIPN treatment trial by Smith et al. [154] of patients with established painful CIPN found an effect of duloxetine on pain severity, suggesting that focusing on pain rather than neuropathy in general could improve assay sensitivity. Of course, the fact that the trial by Smith et al. found an effect of duloxetine could be due to multiple factors other than the primary outcome measure, such as trial size and the fact that it was a treatment trial executed solely after chemotherapy was discontinued, eliminating the variability in neuropathy symptoms caused by changes in chemotherapy dosing during treatment. Cancer patients are often treated with other agents that can cause pain, such as antiestrogen or radiation therapy. In order to minimize the effect that such treatments have on outcome measures of CIPN, patients should be educated on the types of pain caused by neuropathy and instructed to consider only these types of pain, for example, only pain localized to their hands and feet.

A recent meta-analysis by Seretny et al. [151] found that the average reported prevalences of CIPN at 3 and 6 months after termination of chemotherapy were 60% (95% CI: 36% - 82%) and 30% (95% CI: 6.4% - 54%), respectively. However, these estimates were based on relatively few studies (i.e., 4 and 5, respectively) and are highly variable. These data suggest that CIPN symptoms are still naturally decreasing at 3 months after chemotherapy; therefore, 6 months after chemotherapy would be a reasonable time point to assess the effects of a CIPN prevention treatment, although some patients might still have resolution of their pain after this point. However, because these studies did not assess pain specifically, which could have a lower prevalence at both 3 and 6 months after chemotherapy, 3 months should also be considered as an assessment time point given that 3 months is largely considered the minimum duration of pain that is considered to be chronic [48,112]. Previous CIPN prevention studies have assessed neuropathy at 1 month [63, 128], 6 weeks [167], and 3 months [8,9,129,141] after the cessation of chemotherapy. However, only one of these trials declared the chronic CIPN outcome at the chosen time point the primary outcome of the study [141]. An interesting secondary analysis could also examine the “time to recovery” of neuropathic pain after cessation of chemotherapy within the subset of patients that developed a pre-specified level of pain. This type of outcome was used to assess chronicity of neuropathy up to 20 months after cessation of chemotherapy with concurrent gabapentin or placebo treatment [114].

A challenge that is unique to the CIPN prevention model is that although everyone in the study may be prescribed the same or one of a few chemotherapy regimens, chemotherapy is often modified or stopped because of side effects, including neuropathy. The cumulative dosage of chemotherapy is highly associated with neuropathy [7,177] and thus termination of chemotherapy after different dosages can introduce variability in neuropathy outcomes, including pain, at any given time after cessation of chemotherapy. Some studies have dealt with this by eliminating participants who do not receive a pre-specified minimum dosage of chemotherapy [63,128,129,167]. However, this practice could bias the treatment effect estimate because modifications in cumulative chemotherapy dosage could be affected by the investigational treatment; this issue should be carefully considered when developing the statistical analysis plan.

5. Conclusions

Although the preventing chronic pain would have substantial public health benefits, few preventive interventions have been developed. To facilitate the design of clinical trials that would examine the efficacy of such interventions, we have reviewed and discussed research designs and other considerations for such trials. We highlighted 4 models, but these considerations are widely applicable to any pain prevention model in which patients at relatively high risk of developing chronic pain can be identified (see Table 1 for a summary of major considerations). It must be emphasized that many of these recommendations are not based on systematic research, but on published chronic pain prevention and treatment trials and the experience and expertise of the meeting participants. The fact that the majority of the meeting participants were from North America could be considered a limitation. However, we feel that this is unlikely given that the recommendations focus on trial design rather than treatment recommendations or policy considerations. We hope that the

suggestions made in this article will stimulate interest in the prevention of chronic pain and facilitate the development of efficacious and safe preventive interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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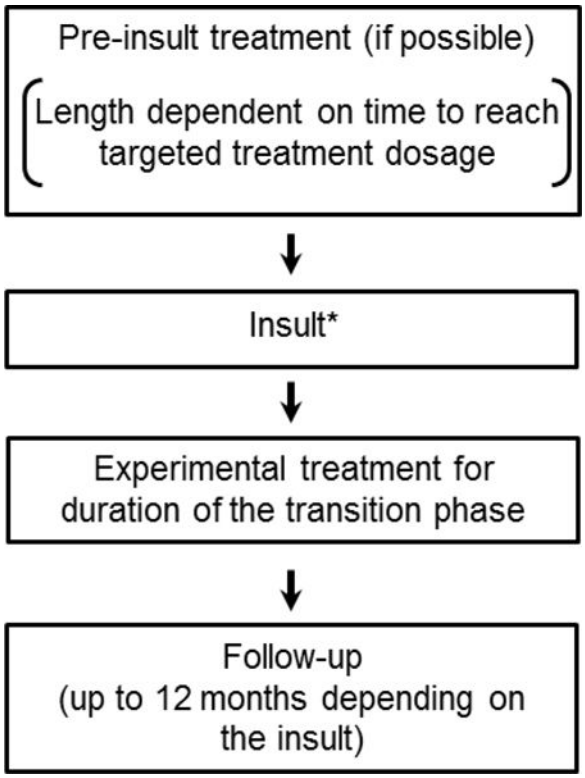

Figure 1. General chronic pain prevention design schema

*Insult models include surgery, disease (e.g., herpes zoster), injury (e.g., acute low back injury), and toxic exposure (e.g., chemotherapy).

Table 1

Recommendations.

Models	Treatment timing	Outcome measures	Assessment timing
CPSP	• Preoperative • Peri-operative • Duration of acute pain recovery (based on natural history of recovery for each surgery)	• Presence vs. absence of pain • Presence vs. absence of “clinically meaningful” pain • Pain intensity at rest • Pain intensity upon movement and specific activities (well defined) • Pain qualities Secondary endpoints: physical and emotional functioning	• 24-48 hours post-surgery • 3, 6, and 12 months • Surgery-specific times based on natural history of acute to chronic pain transition
PHN	• As soon as possible after rash onset (but ≤ 7 days) • Duration of acute HZ pain (≤ 30 days from rash onset)	• Presence vs. absence of pain in the area of the rash • Presence vs. absence of “clinically meaningful” pain in the area of the rash • Pain intensity at HZ rash location • Pain qualities at HZ rash location Secondary endpoints: physical and emotional functioning	• 3-4 months after rash onset
CLBP	• As soon as possible after an acute back pain episode (within 3 weeks) • Duration of acute pain (~ 3 months)	• Presence vs. absence of chronic pain as defined by NIH Task Force [37] • Pain intensity • AUC of pain assessments between 3 months and final time point Secondary endpoints: physical and emotional functioning	• 3, 6, and 12 months
Painful CIPN	• Pre-chemotherapy • Duration of chemotherapy (either daily or only proximal to chemotherapy infusions)	• Presence vs. absence of pain • Presence vs. absence of “clinically meaningful” pain Secondary endpoints: physical and emotional functioning	• 3 and 6 months

Chronic post-surgical pain (CPSP), postherpetic neuralgia (PHN), herpes zoster (HZ), chronic low back pain (CLBP), chemotherapy-induced peripheral neuropathy (CIPN), area under the curve (AUC)