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Accelerating the Development of Improved Analgesic Treatments: The ACTION Public–Private Partnership

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Abstract

There has been considerable progress identifying pathophysiologic mechanisms of neuropathic pain, but analgesic medications with improved efficacy, safety, and tolerability still represent an unmet public health need. Numerous treatments examined in recent randomized clinical trials (RCTs) have failed to show efficacy for neuropathic pain, including treatments that had previously demonstrated efficacy. This suggests that at least some negative results reflect limited assay sensitivity of RCTs to distinguish efficacious treatments from placebo. Patient characteristics, clinical trial research designs and methods, outcome measures, approaches to data analysis, and statistical power may all play a role in accounting for difficulties in demonstrating the benefits of efficacious analgesic treatments vs placebo. The identification of specific clinical trial characteristics associated with assay sensitivity in existing data has the potential to provide an evidence-based approach to the design of analgesic clinical trials. The US Food and Drug Administration recently launched the Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) public-private partnership, which is designed to facilitate the discovery and development of analgesics with improved efficacy, safety, and tolerability for acute and chronic pain conditions. ACTION will establish a collaborative effort to prioritize research objectives, develop a standardized analgesic database platform, and conduct methodologically focused studies to increase the assay sensitivity and efficiency of analgesic clinical trials. The results of these activities have the potential to inform and accelerate the development of improved pain management interventions of all types, not just pharmacologic treatments.

Key Words. Neuropathic Pain; Chronic Pain; Pharmacologic Treatment; Randomized Clinical Trials; Assay Sensitivity

Introduction

Almost 30 years ago, Peter Watson and colleagues published the first double-blind placebo-controlled randomized clinical trial (RCT) of a pharmacologic treatment for patients with neuropathic pain [1]. Since that time, a steadily increasing number of efficacious medications with diverse mechanisms of action have been identified for patients with neuropathic pain [2–6]. Unfortunately, these treatments have significant limitations. In placebo-controlled RCTs, approximately 50–60% of patients administered these medications experience pain reductions of ≥30%, which can be considered "moderately clinically important" [7], with "substantial" pain reductions of ≥50% occurring in no more than 40–50% of patients. These figures demonstrate the presence of a significant public health need for treatments that would provide pain relief to larger percentages of patients with neuropathic pain (e.g., 80% of patients experiencing pain reductions of ≥30%) or that would provide greater magnitudes of relief for the patients who do respond to treatment (e.g., pain reductions of ≥75% in 40–50% of patients). Similar limitations in the treatment effect sizes of existing analgesic medications are also found for other chronic pain conditions, for example, osteoarthritis and low back pain.

In addition to limitations of efficacy, there are considerable undesirable side effects and safety risks associated with many of the available pharmacologic treatments for neuropathic pain [2–6] and other chronic pain conditions [8]. Consequently, there is an equally great need for treatments with greater tolerability and safety (and few or no drug interactions). Finally, because most of the RCTs that have provided evidence of the efficacy of neuropathic pain treatments have been conducted in patients with either painful diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN), greater attention is needed to identifying efficacious treatments for other types of peripheral

neuropathic pain and for central neuropathic pain conditions, which have been studied relatively rarely [2–6].

The limitations of existing pharmacologic treatments for neuropathic pain provide a compelling impetus for the development of medications with improved efficacy, safety, and tolerability. Considerable progress has occurred in understanding the pathophysiologic mechanisms of neuropathic pain [9–11] and substantial effort and resources have been devoted to the identification of novel treatments. However, success in developing improved pharmacologic treatments has been modest at best. There are many potential explanations for this [12], including limitations of animal models of pain [13–15] and of early "proof of concept" studies in human volunteers and in neuropathic pain patients. In addition, some existing compounds may have limited or no efficacy or important safety risks, requiring the development of novel medications with different mechanisms of action. Furthermore, because it is not currently possible to identify the pathophysiologic mechanisms of pain in individual patients, treatments with mechanism(s) of action that target specific pain mechanisms cannot be studied in the subgroups of patients in whom they may be most likely to be efficacious [9].

Highlighting these challenges in developing improved treatments for neuropathic pain is the observation that the proportion of analgesic RCTs in which medications have failed to show statistically significant superiority to placebo in patients with neuropathic pain appears to be increasing [12,16,17]. Several of these trials have investigated medications with well-established efficacy in the conditions that were studied [18–20], including the US Food and Drug Administration (FDA) approved indications, which suggests that some of these results may reflect a failure of the clinical trials themselves to demonstrate analgesic effects. Because negative trials often remain unpublished [21–23], such failures to demonstrate analgesic efficacy are probably more common than the literature would suggest, which could lead to an overestimation of the treatment effects of existing medications.

The modest progress to date in developing improved analgesics and the negative results of many recent clinical trials have not escaped the attention of FDA, which recently launched the Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) public-private partnership [12,24]. The mission of this collaborative effort is to identify, prioritize, sponsor, coordinate, and promote innovative activities—with a special interest in optimizing clinical trials—that will expedite the discovery and development of improved analgesic treatments for the benefit of the public health. In the remainder of this article, we briefly review considerations that led to the development of this public health initiative and describe some of the activities it will undertake, including providing the foundation for an evidence-based approach to analgesic clinical trial design. Although our focus is on analgesic medications, many of the issues involving clinical trials are applicable to devices and other non-pharmacological interventions, including rehabilitative approaches.

The Interpretation of "Negative" Clinical Trials

Assay sensitivity is "a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment" [25], which typically refers to establishing a statistically significant difference in favor of an active treatment vs placebo in an RCT (also termed "responsiveness to treatment effects"). Statistically significant differences for truly efficacious treatments can be considered "true positive" results, which provide the foundation for evidence-based approaches to treatment. Statistically significant differences for truly *non-efficacious* treatments can be considered "false positive" results. Such outcomes can reflect a chance occurrence (i.e., Type I error) as well as various biases or flaws in the design, analysis, and interpretation of the trial, which have received a great deal of attention in the literature [26] and will not be considered further in this article.

When statistically significant differences are not found, one possibility is that the active treatments are not efficacious, and that these are "true negative" results. However, it is also possible that such outcomes reflect inadequate assay sensitivity, in which case they can be considered "false negative" results. False negative outcomes have received considerably less attention in the literature than false positive results, and can reflect a chance occurrence (i.e., Type II error) as well as various patient, study, and statistical factors that could contribute to inadequate assay sensitivity.

As noted in the introduction, RCTs of analgesic medications with well-established efficacy have failed to show statistically significant superiority to placebo in conditions in which efficacy had previously been demonstrated [18–20]. The outcomes of these trials suggest that false negative results can occur in analgesic RCTs, which has major implications not only for developing improved analgesic treatments but also for clinical practice. For example, pharmacologic treatments approved by regulatory agencies and generally considered first- or second-line for the treatment of neuropathic pain [2,3] have not shown efficacy in several neuropathic pain conditions. Specifically, two RCTs failed to show efficacy for amitriptyline [27,28] in patients with painful HIV neuropathy, and recent trials of topical lidocaine [29] and pregabalin [30] in these patients were also negative. Similarly, there have been failures to show efficacy for nortriptyline [31], amitriptyline [32], and gabapentin [33] in chemotherapy-induced peripheral neuropathy, and pregabalin [34] and nortriptyline, morphine, and their combination [35] in lumbosacral radiculopathy. If these results represent a true lack of efficacy, then patients with these neuropathic pain conditions should not be treated with these medications, which may be associated with undesirable side effects, safety risks, and costs. However, if these are false negative results that reflect a lack of assay sensitivity of these RCTs, then effective treatments that could provide meaningful relief might not be considered for patients with these conditions, depriving them of potential benefits.

The explanation for failures of RCTs of efficacious analgesic treatments is currently unknown. Research designs, methodological features, patient characteristics, outcome measures, data analysis methods (including strategies for missing data), and statistical power may all play a role in accounting for difficulties in demonstrating the benefits of efficacious analgesic treatments vs placebo [12,18,36–38]. Perhaps the most common explanation for failed trials is the presence of greater than expected improvement in placebo groups, which could be due to multiple factors, including placebo effects, natural history, regression to the mean, and various study characteristics [39]. For this to be a valid explanation of study failure, however, whatever factors that account for increased improvement in the patients administered placebo must not contribute to a comparable increase in improvement in the patients administered active treatment, otherwise, both groups would simply show greater levels of improvement without any decrease in the group difference occurring.

Regulatory Science and the Transformation of Clinical Trials

A recent report from the Institute of Medicine (IOM), "*Transforming Clinical Research in the United States: Challenges and Opportunities*" [40] discusses a number of important issues involving the performance of clinical trials, focusing on treatments for cardiovascular disease, depression, cancer, and diabetes, but having equally important implications for analgesic trials. The report documents dramatic changes that have occurred in the past three decades in the way in which clinical trials are conducted and in the types of patients who are participating in these trials, and some of these changes could have an influence on clinical trial outcomes. For example, the report emphasizes the challenges facing investigators in academic medical centers [40], one consequence of which appears to be a decrease in the number of academic sites participating in analgesic trials and a shift to private practice sites, in which financial incentives might play a greater role (and investigator interest in and commitment to the trial may be less [40]). Study sites are often encouraged to increase the numbers of subjects they enroll with offers of financial and other incentives, and this may alter patient selection and other study procedures. If aggressive subject enrollment contributes, for example, to the randomization of less severe or more placebo responsive patients, such practices could ultimately compromise assay sensitivity and explain the failure of some RCTs to demonstrate efficacy [41].

The IOM report also documents the globalization of clinical trials, with the percentage of U.S. investigators in the global investigator workforce declining from 85% in 1997 to 57% in 2007 [40]. Unfortunately, little attention has been paid to the impact of national differences in health care systems, including access to health care providers, on the assay sensitivity of clinical trials; in this regard, it is interesting to note that national and regional differences in placebo group improvement have been reported in analyses of RCTs of painful DPN [42] and fibromyalgia [43], as well as in trials of anxiety and depressive disorders [44].

In addition to changes in investigators and sites, it is very likely that other changes have occurred in the characteristics of patients participating in analgesic trials. For example, because of the larger number of efficacious medications that are now available for neuropathic pain—including recognition of the efficacy of opioid analgesics only within the past 10 years—patients in the community who presently are willing to participate in a placebo-controlled RCT may be refractory to a large number of existing medications and may therefore be less likely to respond to a new treatment than was true in the past. It is also possible that patients currently willing to participate in analgesic trials have lower levels of symptom severity than was true in the past, a hypothesis that might also explain increasing levels of placebo group improvement over time in other therapeutic areas [45,46]. The IOM report notes that subjects participating in RCTs of antidepressant medications for depression are often "symptomatic volunteers," that is, individuals who respond to an advertisement but who have not sought any treatment in the community, and therefore, the "clinical trial is the patient's only interaction with the treatment setting" [40]. Such individuals are likely to be quite different compared with patients receiving treatment in actual clinical practice, having fewer medical co-morbidities and possibly less severe depression. The report also describes the existence in psychiatry trials of "professional patients"—individuals who participate in multiple trials as a source of income and medication—noting the example of a 300-patient schizophrenia trial in which 30 individuals were found to have been randomized to the same study by multiple study sites [40].

The extent to which such temporal changes in study investigators, sites, and patients are contributing to a decrease in the assay sensitivity of analgesic clinical trials is unknown. But concerns about the overall state of clinical research in the United States and the clinical trial enterprise in particular have provided the impetus for proposing the development of a clinical trial infrastructure in the United States [40]. Such an infrastructure would provide a permanent network of resources (including sites, investigators, and staff), expertise, and funding for clinical trials that would replace the ad hoc manner in which clinical trials are currently conducted. Although this proposal has much to recommend it, there are considerable obstacles to its implementation, not least of which is the availability of federal funding for such efforts.

Because progress achieving this overarching vision of a transformed clinical trial enterprise will not be rapid, initiatives that have a greater potential for shorter term accomplishments have also been proposed. Woodcock and colleagues [47] have described the FDA's Critical Path Initiative and the role of public-private partnerships in modernizing the methods by which medical treatments are developed, evaluated, manufactured, and used. They note that such a public-private partnership for pain "may

be the catalyst that is needed to enhance translation of scientific opportunities into improved pain relief for chronic diseases and their associated symptoms." Emphasizing the need to improve the development process for analgesic medications, Woodcock [8] subsequently noted that research into better designs for pain trials might identify "highly effective drugs with more easily managed risks"; this could occur by increasing assay sensitivity or study efficiency, thereby making it possible for treatments with novel mechanisms of action to be made available to the public more rapidly.

With these considerations providing the context, the FDA recently announced a "Regulatory Science Initiative" [48,49], in which regulatory science is defined as the "science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products." Importantly, the rationale, methods, and objectives of regulatory science seem to apply equally well to all treatments, not just FDA-regulated products, and this endeavor could therefore be considered more generally "therapeutics development science."

The development of improved pain medications was highlighted as one of the areas in which regulatory science could have a lasting impact, and it was argued that "We are facing a global epidemic of prescription pain medicine abuse and misuse. At the same time, patients in agonizing pain are often left untreated. New pain pathways have been discovered and new medicines are being developed that can help. But to accelerate the delivery of new treatments to patients, we need to find better pain models, measurement tools (including patient-reported assessments) and clinical trial designs to enable development of effective medications with less potential for abuse [49]."

One of the key aspects of the FDA's Regulatory Science Initiative that could accelerate the development of improved analgesics involves using clinical trial data submitted to the FDA "to address fundamental questions about patient subsets who respond in varying ways to new therapies, or for whom a drug is more or less safe [49]." Conducting retrospective analyses of the data from completed clinical trials has the potential to provide greater knowledge of natural history and the effects of specific treatments, which could make clinical development and the evaluation of new treatments more efficient and less risky for patients [49].

A crucial aspect of the FDA's Regulatory Science Initiative involves developing the resources to organize and analyze the numerous and typically large data sets that have been submitted to the agency [49]. This requires "data harmonization and standardization such that comparisons between data can be made effectively [49]." The FDA is aligning with the Clinical Data Interchange Standards Consortium (CDISC) to develop such database standards, which would provide common platforms to facilitate transformation of the data from existing RCTs so that analyses could be conducted of pooled data examining the safety and efficacy of drugs, biologics, and devices. In addition, such common platforms could be used prospectively for regulatory submissions, not only increasing the efficiency of review and analysis of individual trials but also greatly facilitating pooled analyses of the data from different trials.

Consistent with the aims and objectives of the FDA's Regulatory Science Initiative, ACTION was developed to provide a collaborative framework to undertake such analyses of analgesic trials and bridge gaps in the discovery and development of safe and efficacious analgesics [12,24]. Specific objectives of ACTION include: 1) conducting analyses of databases of publicly-available analgesic clinical trials [37,50] and of the raw data from completed RCTs; 2) developing novel methods for analyzing analgesic trial endpoints; 3) developing a CDISC-compliant "STandardized ANalgesic DAtabase for Research, Discovery, and Submissions" (STANDARDS) for the transformation and pooling of data from different analgesic trials; and 4) establishing an ACTION public-private partnership with stakeholders from industry, academia, professional organizations, patient advocacy groups, and regulatory and other government agencies, which will provide a collaborative framework for supporting additional projects to inform analgesic development and trial design and to foster innovation in the development of improved pain treatments.

Developing an Evidence-Based Approach to Analgesic Clinical Trial Design

Recommendations for the design, analysis, and interpretation of RCTs relevant to neuropathic pain treatments have been developed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [36,51–54], the European Federation of Neurological Societies [55], and the International Association for the Study of Pain Neuropathic Pain Special Interest Group [56]. Such recommendations provide the foundation for an evidence-based approach to the design of clinical trials [12], in which relationships between trial characteristics and outcomes are first identified and then used in designing new trials. ACTION will focus on efforts to reduce false negative results and thereby increase assay sensitivity; however, false positive results must also be prevented to the greatest extent possible, and it is critical to ensure that efforts to reduce false negative results do not unintentionally increase the likelihood of false positive results.

In designing and potentially transforming clinical trials [40,47,49], increased understanding of relationships between study methodological features (including patient characteristics) and analgesic trial assay sensitivity—for example, as assessed by standardized effect sizes [57]—could lead to improved research methods [12]. Modifications in the design of analgesic trials have the potential to reduce the likelihood of false negative results and to maximize study efficiency (e.g., by requiring smaller sample sizes). Because assay sensitivity is related to the magnitude of the separation between improvements in the active treatment and placebo groups, an evidence-based

approach to clinical trial design should also include an examination of relationships between study methodological features (including patient characteristics) and placebo group responses. As noted earlier, however, assay sensitivity will only be increased if efforts to reduce placebo group response do not have an equivalent effect on responses to the active treatment.

The results of previous research [12] suggest that various patient characteristics and research methods are associated with analgesic trial assay sensitivity or placebo group responses or both. Unfortunately, relatively few studies have examined these relationships, and further research must be conducted to provide an adequate evidence base for any modification of the methodological features on analgesic RCTs. In pursuing this objective, group-level data across multiple clinical trials in large databases [37,50] and individual trials with patient-level data considered separately and in pooled analyses will provide complementary information.

Patient, study design, and study site characteristics constitute three broad domains of factors that can be examined as potential correlates of study outcome [12]. Patient characteristics include, for example, diagnosis, pain duration, baseline pain intensity, medical and psychiatric co-morbidities, and various psychosocial factors. Study design characteristics include, for example, research design (e.g., parallel group vs crossover), study duration, outcome measures, and statistical methods. Finally, study site characteristics include, for example, sources of patient referrals, number and location of sites included in the trial, and site investigator and staff experience and incentives.

Because many of these patient, study design, and study site characteristics are associated with each other, multivariate analyses of the relationships between these factors and both assay sensitivity and placebo group improvement will need to be conducted [58,59]. These analyses may be limited by the frequency with which the patient, design, and site factors were ascertained or reported. In addition, trial heterogeneity and representativeness, as well as the criteria used for determining trial outcomes, must all be examined carefully [54,60].

Methods of statistical analysis are a critically important component of the design of an RCT, and the analysis of analgesic trial data has received relatively limited attention in the pain literature. The statistical methods used to analyze the data from a trial can have a major impact on the estimated treatment effects, and one major issue involves missing data. There are many reasons for missing data in clinical trials, with as many as 30–60% of patients withdrawing from analgesic trials and failing to provide complete outcome data [18,61]. For this reason, the choice of an approach to be used for the treatment of missing data can have a significant impact on the results. A recent IOM report recommended that imputation methods such as “last observation carried forward” and “baseline observation carried forward”—which have often been used in analgesic trials—should not be used as the primary approach to missing data unless their assumptions are scientifically justified and that analyses of existing clinical trial data should be used to determine how different models perform in different settings [62]. Existing analgesic trial data can be used for these purposes as well as to explore different approaches to the treatment of missing data caused by adverse events, inadequate pain relief, and other reasons.

Finally, despite the value of composite outcome measures for analgesic RCTs that would, for example, combine pain intensity with rescue analgesic medication usage or combine pain intensity with physical functioning, there has been very limited progress in developing such measures [51]. These types of composite measures could have greater responsiveness to treatment effects than unidimensional endpoints—perhaps because patients receiving placebo might be less likely to show improvement in such composite outcomes—and could be developed and validated in analyses of individual and pooled analgesic clinical trial data.

Future Directions

We have proposed that the foundation for an evidence-based approach to analgesic trial design can be provided by analyzing relationships between study outcomes patient, study design, and study site characteristics to identify modifiable factors associated with assay sensitivity. Although retrospective analyses of existing data can be used to generate hypotheses, causal relationships cannot be determined from such analyses, which would ideally be followed by methodologically focused trials that would prospectively examine relationships between patient and study characteristics and assay sensitivity.

There are additional approaches to improving the design of analgesic RCTs that might also increase their assay sensitivity. These include patient and staff training, which have received surprisingly little systematic attention in analgesic trials. Pharmaceutical companies, contract research organizations, and academic investigators have occasionally developed such training materials, but these have not been made publicly available, and it is unclear whether their effects on assay sensitivity have been evaluated. Moreover, the use of different approaches for training patients and staff could contribute to inconsistency among study results, but this also cannot be evaluated without information about the specific training procedures that have been used.

Clinical trial research designs that evaluate patient-based and mechanism-based approaches to pain treatment may also improve the assay sensitivity and efficiency of analgesic RCTs. These treatment approaches have the potential to increase the safety and efficacy of novel analgesics by identifying treatments that target specific pain mechanisms rather than disease etiologies [9,47,63,64]. These and other advances in clinical trial design will require highly trained study staff, large numbers of patients willing to

participate in clinical trials, and the development of a national and international clinical trial infrastructure, as already discussed [40].

There is an important trade-off between increasing assay sensitivity—for example, by excluding certain patients or modifying certain study methods—and reducing the generalizability of study results. Limiting enrollment in RCTs to only certain patients could reduce the generalizability of the results to the substantially more heterogeneous patients receiving treatment in the community [65,66], although it is also possible that greater assay sensitivity could be associated with greater generalizability in certain circumstances. These considerations require further attention, especially with respect to the different objectives of proof-of-concept and confirmatory clinical trials and potential advantages of keeping the "balance" between assay sensitivity and generalizability relatively consistent across these different types of clinical trials.

A major component of the ACTION initiative is the development of a public-private partnership (http://www.actionppp.org) that will provide a collaborative framework to prioritize research objectives and conduct methodologically focused studies and other activities to increase the assay sensitivity and efficiency of analgesic clinical trials [12]. Although there are numerous obstacles to the development of improved analgesics we have not discussed—including lack of validated biomarkers and surrogate endpoints, patient heterogeneity, and safety and tolerability issues [8,67,68]—these will also be a target of ACTION's efforts if prioritized by the stakeholders. It is important to emphasize that the results of all of these activities will also be relevant to the development of improved pain treatments of all types, not just pharmacologic treatments. The promise of this approach is that it will ultimately facilitate more efficient development of novel analgesic treatments and thereby improve the lives of patients with acute and chronic pain.

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References

1 Watson CP, Evans RJ, Reed K, et al. Amitriptyline versus placebo in postherpetic neuralgia. Neurology 1982;32:671–3.

2 Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 2007;132:237–51.

3 Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2009 revision. Eur J Neurol 2010;17:1113–23.

4 Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573–81.

5 Dworkin RH, O'Connor A, Audette J, et al. Recommendations for the pharmacologic management of neuropathic pain: An overview and literature update. Mayo Clin Proc 2010;85(suppl):S3–14.

6 de Leon-Casasola O. New developments in the treatment algorithm for peripheral neuropathic pain. Pain Med 2011;12:S100–8.

7 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.

8 Woodcock J. A difficult balance: Pain management, drug safety, and the FDA. N Engl J Med 2009;361:2105–7.

9 Woolf CJ. Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–51.

10 Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neuroplasticity. J Pain 2009;10:895–926.

11 Liu M, Wood JN. The roles of sodium channels in nociception: Implications for mechanisms of neuropathic pain. Pain Med 2011;12:S93–9.

12 Dworkin RH, Turk DC, Katz NP, et al. Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION. Pain 2011;152(3 Suppl):S107–15.

13 Mogil JS, Davis KD, Derbyshire SW. The necessity of animal models in pain research. Pain 2010;151:12–7.

14 Mogil JS. Animal models of pain: Progress and challenges. Nat Rev Neurosci 2009;10:283–94.

15 Rice AS, Cimino-Brown D, Eisenach JC, et al. Animal models and the prediction of efficacy in clinical trials of

analgesic drugs: A critical appraisal and call for uniform reporting standards. Pain 2008;139:243–7.

16 Beydoun A, Shaibani A, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: Results of a dose-ranging study. Acta Neurol Scand 2006;113: 395–404.

17 Vinik AI, Tuchman M, Safirstein B, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. Pain 2007;128:169–79.

18 Katz N. Methodological issues in clinical trials of opioids for chronic pain. Neurology 2005;65:S32–49.

19 Pfizer protocol A0081071. A randomized double-blind, placebo-controlled, parallel-group, multi-center trial of pregabalin versus placebo in the treatment of neuropathic pain associated with diabetic peripheral neuropathy. 2007. Available at: http://www.clinicalstudyresults.org/drugdetails/?drug_name_id=203&indication_keyword=neuropathy&sort=c.company_name&page=2&drug_id=3972 (accessed November 2010).

20 XenoPort, Inc. Phase II results for GSK1838262 (XP13512) reported for neuropathic pain associated with diabetic peripheral neuropathy. Available at: http://phx.corporate-ir.net/phoenix.zhtml?c=187883&p=irol-newsArticle&ID=1280577&highlight= (accessed November 2010).

21 Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: A literature analysis. PLoS Med 2008;5:1348–56.

22 Rowbotham MC. The impact of selective publication on clinical research in pain. Pain 2008;140:401–4.

23 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358:252–60.

24 Rappaport BA, Cerny I, Sanhai WR. ACTION on the prevention of chronic pain after surgery. Anesthesiology 2010;112:509–10.

25 International Conference on Harmonization. E10: Choice of control groups and related issues. 2001. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125912.pdf (accessed January 2011).

26 Fleming TR. Clinical trials: Discerning hype from substance. Ann Intern Med 2010;153:400–6.

27 Kieburtz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. Neurology 1998;51: 1682–8.

28 Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: A randomized controlled trial. JAMA 1998;280:1590–5.

29 Estanislao L, Carter K, McArthur J, Olney R, Simpson D. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. J Acquir Immune Defic Syndr 2004;37:1584–6.

30 Simpson DM, Schifitto G, Clifford DB, et al. Pregabalin for painful HIV neuropathy: A randomized, double-blind, placebo-controlled trial. Neurology 2010;74: 413–20.

31 Hammack JE, Michalak JC, Loprinzi CL, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. Pain 2002;98:195–203.

32 Kautio AL, Haanpää M, Saarto T, Kalso E. Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms. J Pain Symptom Manage 2008;35:31–9.

33 Rao RD, Michalak JC, Sloan JA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A Phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007;110:2110–8.

34 Baron R, Freynhagen R, Tölle TR, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain 2010;150:420–7.

35 Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain 2007;130: 66–75.

36 Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 2010;149:177–93.

37 Dworkin RH, Turk DC, Peirce-Sandner S, et al. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. Pain 2010;150:12–6.

38 Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: Relationship to study characteristics. Neurology 2008;70:263–72.

39 Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain 2008;138:479–83.

40 Institute of Medicine. Transforming Clinical Research in the United States: Challenges and Opportunities.

Washington, DC: The National Academies Press; 2010. Available at: http://www.nap.edu/catalog.php?record_id=12900 (accessed January 2011).

41 Liu KS, Snavely DB, Ball WA, et al. Is bigger better for depression trials? J Psychiatr Res 2008;42:622–30.

42 Tölle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. Eur J Pain 2008;12:203–13.

43 Häuser W, Bartram-Wunn E, Bartram C, Reinecke H, Tölle T. Systematic review: Placebo response in drug trials of fibromyalgia syndrome and painful peripheral diabetic neuropathy—magnitude and patient-related factors. Pain 2011; DOI: 10.1016/j.pain.2011.01.050.

44 Stein DJ, Baldwin DS, Dolberg OT, Despiegel N, Bandelow B. Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram. J Clin Psychiatry 2006;67:1741–6.

45 Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: Variable, substantial, and growing. JAMA 2002;287:1840–7.

46 Stolk P, ten Berg MJ, Hemels MEH, Einarson TR. Meta-analysis of placebo rates in major depressive disorder trials. Ann Pharmacother 2003;37:1891–9.

47 Woodcock J, Witter J, Dionne RA. Stimulating the development of mechanism-based individualized pain therapies. Nat Rev Drug Discov 2007;6:703–10.

48 Hamburg MA. Innovation, regulation, and the FDA. New Engl J Med 2010;363:2228–32.

49 Department of Health and Human Services, U.S. Food and Drug Administration. Advancing Regulatory Science for Public Health. Available at: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf (accessed January 2011).

50 Dworkin RH, Peirce-Sandner S, Turk DC, et al. Outcome measures in placebo-controlled trials of osteoarthritis: Responsiveness to treatment effects in the REPORT database. Osteoarthritis Cartilage 2011;19:483–92.

51 Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

52 Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain 2009;146:238–44.

53 Turk DC, Dworkin RH, Burke LB, et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain 2006;125:208–15.

54 Turk DC, Dworkin RH, McDermott MP, et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. Pain 2008;139:485–93.

55 Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: Revised 2009. Eur J Neurology 2010;17:1010–8.

56 Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152:14–27.

57 Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd edition. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

58 Sterne JAC, Jüni P, Schulz KF, et al. Statistical methods for assessing the influence of study characteristics on treatment effects in "meta-epidemiological" research. Stat Med 2002;21:1513–24.

59 Whitehead A. Meta-Analysis of Controlled Clinical Trials. Chichester: John Wiley and Sons; 2002.

60 Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 2009;361:1963–71.

61 Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. MorphiDex® (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: Three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or recution in tolerance. Pain 2005;115:284–95.

62 National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: The National Academies Press; 2010. Available at: http://www.nap.edu/catalog.php?record_id=12955 (accessed January 2011).

63 Maier C, Baron R, Tolle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150:439–50.

64 Scholz J, Mannion RJ, Hord DE, et al. A novel tool for the assessment of pain: Validation in low back pain. PLoS Med 2009;6:e1000047.

65 Rothwell PM. External validity of randomized controlled trials: "To whom do the results of this trial apply?" Lancet 2005;365:82–93.

66 Rothwell PM, Watson CPN. External validity of randomized controlled trials: General principles and lessons from trials in neuropathic pain. In: Casto-Lopes J, ed. Current Topics in Pain: 12th World Congress on Pain. Seattle, WA: IASP Press; 2009:199–220.

67 Kissin I. The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesthesiology 2010;110:780–9.

68 Woolf CJ. Overcoming obstacles to developing new analgesics. Nat Med 2010;11:1241–7.