Published in final edited form as:

Pain. 2017 January ; 158(1): 30–33. doi:10.1097/j.pain.0000000000000653.

Painful chemotherapy-induced peripheral neuropathy: lack of treatment efficacy or the wrong clinical trial methodology?

Jennifer S. Gewandter^{a,*}, Robert H. Dworkin^a, Nanna B. Finnerup^b, Nimish Mohile^c

^aDepartment of Anesthesiology, University of Rochester, Rochester, NY, USA

^bDepartment of Clinical Medicine, The Danish Pain Research Center, Aarhus, Denmark

^cDepartment of Neurology, University of Rochester, Rochester, NY, USA

It is often concluded that chemotherapy-induced peripheral neuropathy (CIPN) is non-responsive to many medications with demonstrated efficacy in other chronic peripheral neuropathic pain conditions. This conclusion is based on the fact that most clinical trials of these medications in CIPN have failed to demonstrate a significant treatment effect [4,8,11]. One hypothesis to explain these results is that painful CIPN may have different pathophysiologic mechanisms than other types of neuropathic pain [13,18]. However, only 7 published randomized clinical trials (RCTs) have tested the efficacy of treatments for CIPN, and only 4 of those tested treatments with demonstrated efficacy in other neuropathic pain conditions [8]. Furthermore, as we describe in this review, the trials that have evaluated the efficacy of neuropathic pain treatments (e.g., gabapentin, tricyclic antidepressants) for CIPN have typically not evaluated pain, but rather used variable combinations of “general” peripheral neuropathy symptoms, including pain, dysesthesias, and paresthesias (Table 1).

Primary objectives

To evaluate the analgesic effects of a treatment on painful CIPN, pain must be evaluated separately from the other symptoms associated with neuropathy. The primary outcome measures used in the published CIPN trials often assessed general neuropathy symptoms in the same measure, rather than pain alone. The composite measures used in these trials included numeric rating scales (NRS) or visual analogue scales (VAS) of some combination of pain, numbness, or tingling; the Eastern Cooperative Oncology Group neuropathy scale (ENS) [14]; the National Cancer Institute–Common Toxicity Criteria (NCI-CTC) [20]; and the sensory subscale of the European Organization for Research and Treatment of Cancer Quality of Life – Chemotherapy-induced peripheral neuropathy (EORTC-CIPN-20) [15]).

Three out of 6 of the trials that failed to demonstrate a significant treatment effect on general neuropathy symptoms did not assess the effect of the treatment on pain separately. Of the 3 studies that assessed pain separately, 2 included a pain scale as one of two measures that were declared primary (in both cases the second primary outcome was one of general

*Corresponding Author Jennifer Gewandter, 601 Elmwood Ave, Box 604, Rochester, NY 14609, Tel: +1 585 276 5661, Fax: +1 585 244 7271, Jennifer_gewandter@urmc.rochester.edu.

Conflicts of interest statement

neuropathy symptoms), and 1 assessed pain only as a secondary outcome. Furthermore, only 2 of the studies that investigated a treatment with known efficacy in other neuropathic pain conditions included pain as a separate outcome [17,19] and 1 of those [19] found a significant treatment effect for duloxetine in patients with painful CIPN (Table 1).

Importantly, the evidence supporting the efficacy of existing neuropathic pain treatments is based on trials that evaluated the *pain* associated with peripheral neuropathy conditions such as painful diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) and not general neuropathy symptoms. Most available treatments for neuropathic pain, including those evaluated for efficacy in CIPN, are symptomatic pain treatments with no known disease-modifying or symptomatic effects on non-painful symptoms. Therefore, existing neuropathic pain treatments would not be predicted to improve non-painful neuropathy symptoms. In fact, only one medication (i.e., tafamidis) is approved for a peripheral neuropathy indication by the European Medicines Agency and this approval is specifically for transthyretin familial amyloid polyneuropathy. No medications are approved by the Food and Drug Administration for a peripheral neuropathy indication.

It is worth noting that the Smith et al. trial [19] did demonstrate a treatment effect of duloxetine on a secondary outcome measure of peripheral neuropathy, the FACT/GOG-Ntx [3]. The FACT/GOG-Ntx is a composite measure that includes assessments of pain, numbness, tingling, and other symptoms. These data suggest that duloxetine may have efficacy for general peripheral neuropathy symptoms associated with CIPN in addition to efficacy for pain; however, the effect of duloxetine could be explained by FACT/GOG-Ntx pain-related items. Additionally, given important methodological differences among the CIPN trials, this apparent effect of duloxetine on general peripheral neuropathy symptoms in CIPN does not suggest that the other trials are truly negative for general neuropathy symptoms.

Inclusion criteria

In order to assess the effects of a treatment on pain, it is essential that all of the patients included in a clinical trial have at least moderate pain. Enrolling patients with only mild pain can impair detection of treatment efficacy due to a “floor effect” (i.e., an inability to observe a decrease in symptoms if the condition is already too mild at baseline) [6]. For example, a pooled analysis of 3 trials of patients with painful DPN and a meta-analysis of neuropathic pain trials both demonstrated that lower baseline pain scores were associated with decreased assay sensitivity (i.e., ability to demonstrate a difference between groups in a clinical trial) [7,21].

Only one of the CIPN trials used a minimum average pain score (i.e., 4 out of 10 on a numeric rating scale (NRS)) as an inclusion criterion [19]. The other trials used either (1) “painful paresthesiae” with no minimum pain requirement specified [10]; (2) either 4 out of 10 for average pain NRS or 1 on the ENS, which does not require pain [16,17]; or (3) 4 out of 10 on an NRS for “pain, numbness, or tingling” [2,9,12] (Table 1).

Of the trials that did not require a minimum pain score for inclusion, and therefore may have included patients who had no pain, the mean baseline average pain scores ranged from 3.6 to 4.2 [16,17]. These mean average pain scores are low for analgesic trials [6], as a mean baseline pain score of 6.0 out of 10 was reported in a meta-analysis of 200 neuropathic pain trials [7]. Furthermore, the mean average pain scores in the only published CIPN trial that had a minimum pain requirement for inclusion were 6.1 and 5.6 in the active and placebo groups, respectively [19].

The trials of gabapentin [17] and lamotrigine [16] did use a 0–10 NRS for average pain as 1 of 2 outcome measures declared to be primary (Table 1). However, because eligible patients were not required to have a minimum pain level and the baseline average pain scores were low, the inability to detect a treatment effect could be due to a floor effect. One study did note that “the subset of patients who had higher pain scores at baseline did not appear to have a preferential benefit with gabapentin when compared with those with lower baseline scores” [17]. However, subgroup analyses like these are underpowered and a non-significant difference between groups should not be interpreted as compelling evidence for lack of treatment efficacy.

Chronicity of pain

Although both acute and chronic CIPN are major unmet treatment needs, they are different conditions for which treatments should typically be assessed in separate clinical trials with homogeneous populations. Three CIPN trials allowed enrollment of both patients who were still receiving neurotoxic chemotherapy and also those who had completed chemotherapy [2,16,17]. When evaluating analgesics known to be efficacious for *chronic* neuropathic pain of other etiologies, enrolling patients still receiving chemotherapy could decrease the ability of the trial to detect effects on chronic painful CIPN. The neuropathy symptoms that occur during chemotherapy, as well their pathophysiologic mechanisms are likely to differ from the symptoms and mechanisms found in individuals who have completed chemotherapy and may not be responsive to treatments that are effective for chronic pain.

CIPN symptoms during chemotherapy are likely to be worsening over time due to higher cumulative dosages of chemotherapy and may also vary depending on the duration of time that has elapsed since the latest dose of chemotherapy [1]. Additionally, symptoms occurring during chemotherapy are more likely to naturally dissipate once chemotherapy is discontinued than are the symptoms experienced by chronic CIPN patients who discontinued chemotherapy at least several months prior [1]. This unstable severity of neuropathy symptoms during chemotherapy and shortly after is likely to add variability to neuropathy outcome measures and could decrease assay sensitivity in trials that recruit CIPN patients while they are still receiving chemotherapy.

Conclusions

Only 4 out of the 7 published clinical trials of patients with chronic CIPN evaluated treatments that are recommended as first-line treatments for neuropathic pain by the International Association for the Study of Pain, Neuropathic Pain Special Interest Group

(NeuPSIG) treatment guidelines [8] (i.e., amitriptyline, duloxetine, gabapentin, and nortriptyline). Thus, only those 4 trials would be expected to demonstrate efficacy if chronic painful CIPN responds to the same treatments as other chronic neuropathic pain conditions. Furthermore, of these 4 trials, the one that successfully demonstrated the efficacy of the treatment on neuropathic pain (i.e., duloxetine) was the only one that (1) used a primary outcome measure that assessed only pain, (2) used a minimum pain intensity for the principal inclusion criterion, and (3) included only patients who had completed chemotherapy [19]. It cannot be determined whether the other trials are falsely or truly negative for the treatment of peripheral neuropathy, but it is clear that they do not evaluate the efficacy of the treatments for neuropathic pain. Thus, it should not be concluded that painful CIPN is pathophysiologically different than other types of peripheral neuropathic pain based on the non-significant results of the published CIPN trials. Future trials that aim to assess symptomatic chronic pain treatments should utilize validated pain measures for the primary efficacy analysis (e.g., 0 – 10 NRS daily diary for pain) [5]. The pain measure should specify whether participants are to rate their worst or average pain and participants should be instructed to rate only the pain in their hands and / or feet that has developed since their chemotherapy was initiated. These trials should include only patients who have completed chemotherapy at least 3 months prior to enrollment and who meet a minimum baseline pain requirement (e.g., 4 on a 0 – 10 NRS for average pain) [6]. Additionally, a neurological examination is recommended to confirm that eligible participants have peripheral neuropathic pain associated with CIPN. Such trials must be conducted before chronic painful CIPN is declared refractory to current or future neuropathic pain treatments.

Acknowledgments

Jennifer S. Gewandter has received compensation from Immune Pharmaceuticals for consultation on CIPN clinical trial design. Robert H. Dworkin, PhD, has received in the past 12 months research grants and contracts from US Food and Drug Administration and US National Institutes of Health, and compensation for activities involving clinical trial research methods from Abide, Adynxx, Aptinyx, Astellas, Biogen, Dong-A, Glenmark, Hope, Hydra, Immune, Medavante, Novartis, NsGene, Olatec, Periphagen, Phosphagenics, Reckitt Benckiser, Relmada, Semnur, Spinifex, Syntrix, Teva, Trevena, and Vertex.

References

1. Argyriou AA, Bruna J, Marmioli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. *Crit Rev Oncol Hematol* 2012;82:51–77. [PubMed: 21908200]
2. Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD 3rd, Kugler JW, Hoff KL, Reddy PS, Rowland KM Jr., Riepl M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer* 2011;19:833–41. [PubMed: 20496177]
3. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, et al. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer* 2003;13:741–748.
4. Dworkin RH, O'connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmadier KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2010;85:S3–14.
5. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR,

- Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9–19. [PubMed: 15621359]
6. Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I, Jensen MP, Katz NP, Raja SN, Rappaport BA, Rowbotham MC, Backonja MM, Baron R, Bellamy N, Bhagwagar Z, Costello A, Cowan P, Fang WC, Hertz S, Jay GW, Junor R, Kerns RD, Kerwin R, Kopecky EA, Lissin D, Malamut R, Markman JD, McDermott MP, Munera C, Porter L, Rauschkolb C, Rice AS, Sampaio C, Skljarevski V, Sommerville K, Stacey BR, Steigerwald I, Tobias J, Trentacosti AM, Wasan AD, Wells GA, Williams J, Witter J, Ziegler D. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012;153:1148–58. [PubMed: 22494920]
 7. Dworkin RH, Turk DC, Peirce-Sandner S, He H, McDermott MP, Farrar JT, Katz NP, Lin AH, Rappaport BA, Rowbotham MC. Assay sensitivity and study features in neuropathic pain trials: An ACTTION meta-analysis. *Neurology* 2013;81:67–75. [PubMed: 23700332]
 8. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573–81. [PubMed: 20705215]
 9. Gewandter JS, Mohile SG, Heckler CE, Ryan JL, Kirshner JJ, Flynn PJ, Hopkins JO, Morrow GR. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer* 2014;22:1807–14. [PubMed: 24531792]
 10. Hammack JE, Michalak JC, Loprinzi CL, Sloan JA, Novotny PJ, Soori GS, Tirona MT, Rowland KM Jr., Stella PJ, Johnson JA. Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy. *Pain* 2002;98:195–203. [PubMed: 12098632]
 11. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2014;32:1941–67. [PubMed: 24733808]
 12. Kautio AL, Haanpaa M, Leminen A, Kalso E, Kautiainen H, Saarto T. Amitriptyline in the prevention of chemotherapy-induced neuropathic symptoms. *Anticancer Res* 2009;29:2601–6. [PubMed: 19596934]
 13. Majithia N, Temkin SM, Ruddy KJ, Beutler AS, Hershman DL, Loprinzi CL. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons. *Support Care Cancer* 2016;24:1439–47. [PubMed: 26686859]
 14. Oken MM, Creech RH, Tormey DC, Horton K, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–55. [PubMed: 7165009]
 15. Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, Hoang-Xuan K, Lanteri-Minet M, Grant R, Huddart R, Moynihan C, Maher J, Lucey R. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *Eur J Cancer* 2005;41:1135–9. [PubMed: 15911236]
 16. Rao RD, Flynn PJ, Sloan JA, Wong GY, Novotny P, Johnson DB, Gross HM, Renno SI, Nashawaty M, Loprinzi CL. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled trial, N01C3. *Cancer* 2008;112:2802–8. [PubMed: 18428211]
 17. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevic DA, Warner DO, Novotny P, Kutteh LA, Wong GY. 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. [PubMed: 17853395]
 18. Sisignano M, Baron R, Scholich K, Geisslinger G. Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. *Nat Rev Neurol* 2014;10:694–707. [PubMed: 25366108]
 19. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013;309:1359–67. [PubMed: 23549581]

20. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176–81. [PubMed: 12903007]
21. Ziegler D, Pritchett YL, Wang F, Desai D, Robinson MJ, Hall JA, Chappell AS. Impact of disease characteristics on the efficacy of duloxetine in diabetic peripheral neuropathic pain. *Diabetes Care* 2007;30:664–9. [PubMed: 17327338]

Table 1:

CIPN treatment trials

Article	Treatment	Design	N	Major inclusion criteria	Primary outcome measure	Results	Notes
Hammack et al., 2002	Nortriptyline (75–100mg/day as tolerated)	Crossover; 4 weeks treatment	57 randomized; 51 analyzed	• “Painful paresthesiae for at least 1 month attributed to cisplatin-induced neuropathy”	VAS and VDS for pain/tingling	Not significant	• 15% and 12% in the 2 groups were actively receiving chemotherapy at the time of enrollment
Rao et al., 2007	Gabapentin (2700mg/day as tolerated)	Crossover; 6 weeks treatment	115 randomized; 68 analyzed	• Either 4 out of 10 on pain NRS or 1 on Eastern Cooperative Oncology Group neuropathy scale (ENS) [0 = none; 1 = mild paresthesias, loss of deep tendon reflexes] • Patients currently receiving chemotherapy or who had completed chemotherapy	0–10 NRS for “average pain” and ENS	Not significant	• Mean baseline average NRS scores by group were 4.3 and 3.6 • Percentage receiving neurotoxic chemo at enrollment not reported
Kautio et al., 2008	Amitriptyline (10mg – 50mg/day as tolerated)	Parallel group; 8 weeks treatment	44 randomized (terminated early); 42 analyzed	• 3 out of 10 on 0–10 NRS of “pain, numbness, or tingling” • All participants currently receiving neurotoxic chemotherapy at enrollment	NCI-CTC	Not significant	• Authors note that no participant had neuropathy over grade 2.
Rao et al., 2008	Lamotrigine (300mg/day)	Parallel group; 10 weeks treatment	125 randomized; 80 analyzed	• Either 4 out of 10 on “average” pain NRS or 1 on Eastern Cooperative Oncology Group neuropathy scale (ENS) [0 = none; 1 = mild paresthesias, loss of deep tendon reflexes] • Patients currently receiving chemotherapy or who had completed chemotherapy	0–10 NRS of “average pain” and ENS	Not significant	• Mean baseline average NRS pain scores by group were 4.2 and 3.6. • 38% and 45% in the 2 groups were actively receiving chemotherapy at the time of enrollment
Barton et al., 2011	Topical amitriptyline (3%), ketamine (1.5%), and baclofen (0.7%) combination	Parallel group; 4 weeks treatment	208 randomized; 150 analyzed	• 4 out of 10 on 0–10 scale of pain, numbness, or tingling. • Patients currently receiving or completed chemotherapy treatment	Sensory subscale of the EORTC-QLQ-CIPN20	Not significant	• 29% and 25% in the 2 groups were actively receiving chemotherapy at the time of enrollment
Smith et al., 2013	Duloxetine (60mg/day)	Crossover; 6 weeks treatment	231 randomized; 187 analyzed	• At least grade 1 sensory pain on NCI-CTC AND 4 out of 10 on “average pain” NRS • Patients completed chemotherapy at least 3 months prior	0–10 NRS of “average pain”	Significant	• Primary analysis is parallel group comparison of first period • Mean baseline average pain scores by group were 6.1 and 5.6
Gewandter et al., 2014	Topical amitriptyline (4%) and ketamine (2%) combination	Parallel group; 6 weeks treatment	462 randomized; 458 analyzed	• 4 out of 10 on NRS of “pain, numbness, or tingling in the hands or feet” • Patients completed chemotherapy at least 1 month prior	0–10 NRS of “pain, numbness, or tingling in the hands or feet”	Not significant	

Eastern Cooperative Oncology Group neuropathy scale: ENS

European Organization for Research and Treatment of Cancer Quality of Life – Chemotherapy-induced peripheral neuropathy-20 (EORTC-CIPN-20)

Note: unless otherwise stated in the publication, it was assumed the number of subjects analyzed was the same as the number who completed the trial

Verbal descriptor scale: VDS

Visual analogue scale: VAS

National Cancer Institute – Common Toxicity Criteria: NCI-CTC

Numeric rating scale: NRS

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript