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Neuropathic pain and other symptoms/signs are both important unmet treatment needs in patients with CIPN

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We would like to thank Kerckhove and colleagues for highlighting an important issue that we did not address in our Topical Review of recent randomized clinical trials (RCTs) conducted in patients with chemotherapy-induced peripheral neuropathy (CIPN). Although we did not discuss the prevalence of neuropathic pain in patients with CIPN, we agree that studies that have assessed pain separately from general neuropathy symptoms suggest that pain occurs less frequently in CIPN patients than do other neuropathy symptoms such as numbness and tingling [Attal N, 2009, Ventzel L, 2016]. Unfortunately, the reported prevalence for general neuropathy symptoms in patients with chronic CIPN varies greatly among studies, as evidenced by the wide confidence intervals of the estimates provided in the recent meta-analysis by Seretny et al. [Seretny M, 2014] (i.e., 3 months post-chemotherapy: 60% prevalence, 95% CI [37% – 84%]; 6 months post-chemotherapy: 30% prevalence [6% – 55%]). Furthermore, few studies have assessed pain separately from other symptoms that occur after completion of chemotherapy, and existing data indicate that the percentage of patients with chronic pain associated with CIPN might be relatively low but could also be quite high. One recent prospective cohort study of 174 cancer patients assessed pain separately from other neuropathy symptoms and found that even after excluding patients who had numbness and tingling before initiating chemotherapy, 28% and 26% of patients receiving oxaliplatin and docetaxel, respectively, reported neuropathic pain 12 months after completing chemotherapy [Ventzel L, 2016]. These data suggest that pain may be present in a substantial percentage of patients long after completion of chemotherapy. Importantly, even if pain associated with CIPN is relatively uncommon, efforts should still be devoted to identifying efficacious treatments. Although recruiting sufficient participants for a phase 3 trial may be challenging if the prevalence is relatively low, one recent trial enrolled 231 CIPN patients with pain of at least 4 on a 0–10 numerical rating scale and demonstrated the superiority of duloxetine vs. placebo [Smith EM, 2013].

We assume that in using the term “antineuropathic treatments,” Kerckhove and colleagues are referring to treatments that target the major symptoms and signs of CIPN, not only peripheral neuropathic pain. We certainly agree that the development of symptomatic and disease-modifying treatments is a very important unmet public health need, not only for

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CIPN but also for other peripheral neuropathies (e.g., diabetic, HIV, idiopathic). However, when designing RCTs, the primary outcome measure should be chosen based on the symptom(s) and/or sign(s) for which the treatment is hypothesized to provide benefit, not on prevalence [Gewandter JS, 2015]. When assessing the effect of treatments with established analgesic efficacy in other indications, pain is the outcome that would be expected to show a benefit of treatment. Therefore pain would typically be the primary efficacy variable and would also be used to determine participant eligibility in the trial. Clinical trials of medications with hypothesized or established efficacy for peripheral neuropathic pain were the focus of our review, not trials of medications thought to have benefits on peripheral neuropathy symptoms in general (e.g., aldose reductase inhibitors in diabetic peripheral neuropathy). Finally, as we argued in our article, if a minimum pain score is not required for study entry and the analysis of the non-pain primary outcome measure or a pain secondary outcome measure fails to reach statistical significance, the trial should not be used as evidence to suggest that an analgesic treatment does not work for pain associated with CIPN or that CIPN is likely mechanistically different than other neuropathic pain conditions. Importantly, patients with painful CIPN should not be denied treatment with analgesic drugs that are efficacious in other neuropathic pain conditions based on results from trials in CIPN not designed to evaluate pain.

We are optimistic that novel symptomatic and disease-modifying treatments with promise for overall CIPN symptoms and signs can be identified in preclinical research, early phase human studies, and from successes in other peripheral neuropathies. The primary outcome for RCTs of such treatments could use composite measures of symptoms and/or signs or measures of individual non-painful symptoms (e.g., numbness, cramping) if the results of early research suggest a particular symptom is the most promising target. Many composite patient-reported outcome measures have been developed for various types of peripheral neuropathy, including CIPN specifically [Cavaletti G, 2010, Gewandter JS, 2016]. Composite measures for CIPN and other peripheral neuropathies can also include clinician-rated signs of peripheral neuropathy (e.g., vibration, tactile sensation) as well as the combination of both patient-reported and clinician-rated items. Studies of the reliability and validity of some composite outcome measures of overall neuropathy symptoms and signs in CIPN are available [Cavaletti G, 2013, Griffith KA, 2010]. Importantly, in one recent, large study evaluating intra-and inter-rater reliability of a set of composite clinician-rated outcome measures, a consensus was achieved regarding how to implement the measures and all of the investigators were trained based on the consensus [Cavaletti G, 2013]. Such steps, which will likely improve intra-and inter-rater reliability, will be imperative for successful implementation of any clinician-based outcome measures in multi-site RCTs. Future studies of the responsiveness to change of these measures are needed to determine their suitability for use in clinical trials.

In conclusion, we very much hope that investigators will continue to pursue the identification of treatments for neuropathic pain and other symptoms/signs of CIPN and we continue to believe that the design of RCTs and their primary outcomes should reflect the hypothesized benefits of the investigational treatment.

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