



Letter to the editor—comments on Kleckner et al. (2018) “Effects of exercise during chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial”

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We read with interest the recent article by Kleckner et al. [1] examining the effects of a 6-week exercise program (EXCAP®) among 355 cancer survivors (breast, lymphoma, colon, lung, and other) on chemotherapy-induced peripheral neuropathy (CIPN). We agree that CIPN is an important patient outcome in the exercise and cancer field. In their trial, the authors concluded “exercise appears to reduce CIPN symptoms in patients receiving taxane-, platinum-, or vinca alkaloid-based chemotherapy.” (p. 1019). In our opinion, while the study shows potentially positive trends, the conclusions drawn by the authors may be somewhat premature.

The authors stated, “Exercise reduced CIPN symptoms of hot/coldness in hands/feet (-0.46 units, $p=0.045$) and numbness and tingling (-0.42 units, $p=0.061$) compared to the control. Exercise reduced CIPN symptoms more for patients who were older ($p=0.086$), male ($p=0.028$), or had breast cancer ($p=0.076$).” (p. 1019). Table 2 and Figure 2 in the Kleckner et al. article show that exercise did not *reduce* these symptoms, and instead these symptoms *increased*. It appears the intervention may have slightly *attenuated* an increase in symptoms in the exercise group, as increases in this group were smaller in magnitude compared to the control group (although the clinical relevance of this attenuation is tenuous). While an attenuation of symptoms is a promising finding, we propose that the authors consider revising their conclusions to more

accurately reflect and describe the data and the results (i.e., symptoms increased, but there was a small attenuation of symptom exacerbation in the exercise group).

In their analyses comparing the two groups on CIPN outcomes, the authors did not adjust for multiple comparisons. This should be considered when interpreting the results of the study, given the alpha 0.05 threshold is for a single comparison and the likelihood of chance findings increases as more comparisons are made. If a Bonferroni correction were applied to the two primary outcomes, an alpha of 0.025 would be the threshold for determining significance ($0.05/2 = 0.025$), and findings presented would not meet the threshold for significance. For the subgroups analyses, adjusted findings would not approach a *trend* signal. If a case is to be made for refraining to adjust for multiple comparisons, other strategies indicating the magnitude of effects should be presented to assist the reader in reaching a reasonable conclusion, such as an effect size [2]. The authors indicated the clinical significance of these effects is *likely*; however, no evidence to support this contention is presented.

To measure CIPN, the authors used two single-item indicators of (a) numbness and tingling, and (b) hot/coldness in hands/feet. Two citations for these items were provided [3, 4] and the authors indicated, “validity and reliability have been demonstrated for similar scales of numbness and tingling for cancer patients.” (p. 1021). Both studies cited examined breast cancer survivors and did not evaluate an item referring to “hot/coldness in hands/feet.” Caution must be taken when administering items validated in other tumor groups for reasons including differing treatment protocols and treatment plans. Comprehensive self-report scales that cover the spectrum of CIPN, with demonstrated reliability and validity, are available for use (e.g., FACT-Taxane [5]). Despite single-item indicators being suspect (e.g., unknown internal consistency, random measurement errors), we recognize the utility of using single-item indicators when evidence suggests the item possesses some degree of predictive validity with respect to the broader construct (in this case, CIPN). Nonetheless,

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measurement of these patient-reported outcomes should not be underestimated.

The authors concluded, “Exercise appears to reduce CIPN symptoms in patients...” (p. 1021). At baseline, when collapsed across both groups, participants on average scored 0.9 for numbness and tingling (exercise 0.72, control 1.06) and 0.8 for hot/coldness (exercise 0.76, control 0.90) out of 10 (0 = not present/no symptoms, 10 = as bad as you can imagine/severe symptoms). For the tingling/numbness item, the Bao et al. study [4] proposed a score of ≥ 1 suggests *mild symptoms*, and scoring below one (< 1) is an indication of *no symptoms*. These baseline scores suggest participants in this trial, on average, were not experiencing CIPN symptoms upon entry into the study. The clinical meaningfulness of simply scoring > 0 is questionable and is not indicated in the literature.

At post-intervention, within groups, changes across the two CIPN items ranged from +0.38 (exercise) to +0.77 (control) across the groups. The between-groups differences on the CIPN items can be interpreted as being negligible (i.e., 0.20 for numbness and tingling, and 0.36 for hot/coldness in hands/feet). Similar to the baseline data, post-intervention data from this study sample strongly suggested that participants, on average, were not experiencing any clinically meaningful CIPN symptoms. We propose that the authors consider tempering their conclusions, examine the magnitude of these small changes, and refrain from indicating that CIPN symptoms were reduced, despite observed increased scores (albeit small). Indeed, a slight attenuation may be indicative, and recognition of this is certainly appropriate and recommended.

The authors noted a “...reduction of prevalence from approximately half of patients in the control group to approximately one third of patients in the exercise group.” (p. 1024). The authors indicated that at baseline, 29.6% and 2.4% of the overall sample reported tingling/numbness, and hot/coldness in hands/feet, respectively (i.e., a score of > 0). Post-intervention percentages were presented for each group for numbness/tingling (exercise 36.5%; control 49.2%) and the hot/coldness outcome (exercise 33.5%; control 45.4%). Without reporting the percentages of the two study groups at

baseline, the reader is unable to determine changes in prevalence of participants reporting a score of > 0 on the CIPN items. We feel describing these changes in prevalence as a *reduction* is misleading and incorrect as prevalence appeared to increase at post-intervention. We propose that including the baseline information from both groups would provide the reader with a more complete understanding of the changes in prevalence.

CIPN is a distressing symptom for many patients with cancer and we understand the urgency for identifying strategies to counter this treatment-related symptom. The authors are to be commended for examining an established home-based exercise program, and the strong sample size and study design.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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