assessment issues should be addressed in the accompanying note through consideration of multiple sources of relevant information.

In addressing the multidimensional nature of the experience of pain, Dr Alcock does not object to the addition of the word "cognitive" to characterize the experience, but demurs on the use of the term "social," suggesting it "may not be well suited to a definition of pain," concluding that terms referring to sensation, thoughts, feelings, and behaviours are sufficient. Nevertheless, he observes that the biopsychosocial framework for pain argues for bidirectional relationships among "pain, biomedical, psychological, and social factors." We note that increasing attention to the neurobiology of human interactions[2,4,7] argues the ubiquity of social factors in human action and decision making. We have an opportunity that should not be missed to explicitly acknowledge the importance of social factors as features of pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Ultramicronized palmitoylethanolamide treatment in central neuropathic pain following longstanding spinal cord injury: try to extinguish the fire after everything was burned

Letter To Editor:

In a recent issue of *PAIN*, Andresen et al.[3] reported the results of a randomized, double-blind, placebo-controlled clinical trial examining the effect of ultramicronized palmitoylethanolamide (PEA-um) as add-on therapy on neuropathic pain following spinal cord injury (SCI), as well as the effects on spasticity and psychological functioning. The ineffectiveness of PEA-um contrasts with current literature describing the beneficial effects of PEA-um in neuropathic pain.[12,13] As the authors discuss, reasons for this negative outcome could relate to several factors (patient heterogeneity regarding causes and levels of SCI, concomitant medications and unresponsiveness to pain treatment). Unfortunately, the study does not provide details on medication dosing or on the length of pharmacological treatment before administration of PEA-um. Given a baseline pain score of 6.4, although most patients were already receiving a large amount of medications for pain and spasticity, it is difficult to expect a beneficial effect of PEA-um. In the trial by Andresen et al, in the PEA-um group, 77.7% of patients were already taking gabapentinoids (in contrast to 54% in the placebo group) along with many other drugs in combination (weak and strong opioids, antidepressants, other drugs) so, probably, they represent a group of patients particularly unresponsive to pain treatments. Furthermore, the timing of treatment effects on glia could be crucial in these patients. There is evidence that glial activation plays a major role in the development and maintenance of neuropathic pain after SCI in an animal model.[9] For this reason, specific treatments aimed to reduce glial activation have been already tested in the early stages of spinal injury.[15] In both treatment groups in the Andresen et al. trial, the duration of time from the trauma is relevant (9.4 years in the PEA-um group, 11.1 years in the placebo group) and makes a therapeutic response to a glial inhibitor unlikely when the glial activation may have already produced permanent structural modifications. Moreover, no explanation is given as to why there was a significant reduction of acetaminophen consumption in the PEA-um group compared with the placebo group. Some experimental data in the animal model of neuropathic pain have shown synergistic activity of PEA combined with acetaminophen and such synergistic effects might explain the observed reduction of acetaminophen consumption in the treatment group.[6] In the trial by Andresen et al, the PEA-um group and the placebo group were not homogeneous with respect to gender. Specifically, in the placebo group, there were only 5 female patients compared with 14 in the PEA-um group. Although the possibility that gender is a predictor of the severity of neuropathic pain is controversial,[4,5] research using an animal model of neuropathic pain showed a different response in regulating pain hypersensitivity mediated by microglia depending on gender.[10] Andresen et al. reported that female gender is a risk factor for the development of neuropathic pain after SCI.[2] In our opinion, therefore, it is necessary that in the clinical pain studies, different groups must be homogeneous with respect to gender. Despite the lack of significant results emerging from the trial of Andresen et al, an ever-growing body of evidence documenting the pain-relieving, anti-inflammatory and neuroprotective actions of PEA should encourage further studies on PEA-um effects in SCI particularly at shorter times postinsult.[1,7,8,11,14]

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Reply

Letter To Editor:

We thank Dr. Polati et al. for their interest in our study. Polati et al. emphasize what we also conclude from our study, namely that ultramicronized palmitoylethanolamide (PEA-um) has no effect as add-on therapy in chronic neuropathic pain after spinal cord injury (SCI), although this does not preclude an effect of PEA in the early stages of SCI or in patients without concomitant treatment.

In some aspects, however, we do not entirely agree with Polati et al. They note, for example, that the negative results of our study contrast with the current literature. However, most studies suggesting an effect of PEA-um in neuropathic pain are preclinical studies, open-label studies, or case reports, and the poor predictive value of preclinical animal models is well known in the field of neuropathic pain.[4] In fact, only 2 randomized, controlled, double-blind studies of PEA in neuropathic pain have been published. Both studies, published in Spanish by the same group, showed an effect of PEA in lumbosciatica,[1,3] but the effect of PEA or PEA-um in other neuropathic pain conditions has not been examined in randomized controlled trials.

Polati et al. also argue that the large number of patients taking medications for pain and spasticity in our study makes it difficult to expect a beneficial effect of PEA-um. This may not necessarily be the case. Two large studies documenting a pain-relieving effect of pregabalin on SCI-related neuropathic pain included patients with a mean pain duration of 9 to 10 years, similar to our study, and the studies also showed that of these patients 91% to 97% received various concomitant drug treatments while looking at only concomitant pain medications, the percentage was between 69% and 76%.[2,5] Polati et al. also point out that the PEA-um and placebo groups were not homogeneous with respect to sex. However, we found no effect of PEA-um when separating the groups into men (n = 49) and women (n = 19).

In conclusion, we agree that although our study showed no effect of PEA-um in chronic neuropathic pain after SCI, it does not provide any data on a possible early preventive effect of PEA-um.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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