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LETTER TO THE EDITOR

Comment on: "Treating Pain in Diabetic Neuropathy: Current and Developmental Drugs"

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Dear Editor

We congratulate Alam et al. [1] on their review of the treatment of painful diabetic peripheral neuropathy (pDPN). An overview of currently available medications and potential future developments is indeed valuable given the increasing prevalence of diabetes, its consequences and the lack of specific pDPN treatment guidelines.

The authors conducted a comprehensive literature search of published articles up to November 2019 and excluded non-relevant articles but did not specify the criteria for disregarding publications. This might have resulted, possibly inadvertently, in incomplete reporting on some of the available treatment options. Specifically, more detailed information on the use of high-concentration capsaicin patch (HCCP) for pDPN would have been appropriate. In this letter, we address this topic to correct some of the misconceptions that may have been created.

In Sect. 5.1, the authors discussed US FDA-approved medications for pDPN and other peripheral neuropathic pain indications. Unfortunately, HCCP, which is approved by the FDA for post-herpetic neuralgia, was not included, and nor was any reference made to its approval in the EU for the treatment of pDPN in 2015 [2]. Unsurprisingly, international consensus guidelines for the treatment of pDPN do not include HCCP, given that three of the five cited guidelines originate from US societies (HCCP is currently not approved by the FDA for pDPN). The cited European Federation of Neurological Societies guidance predates the EU approval, and the UK National Institute for Health and Care Excellence guidance is specific to a non-specialist setting even though HCCP is primarily used in specialist care in the UK. More recently, updated guidelines from the German Association of Neurology [3] and in France [4] recommend topical preparations (lidocaine 5% plaster and HCCP) for focal treatment of neuropathic pain. In our opinion, as HCCP is the only topical treatment currently approved for pDPN in a major region of the world, it is important to inform readers about this treatment option.

The marketing authorization for HCCP in pDPN in Europe was based on a randomized controlled trial [5] that was unfortunately omitted from the current review. This well-controlled trial included 186 patients per treatment arm and showed that commonly reported adverse reactions with HCCP were mostly application site reactions. These data compare favorably with those presented for oral medications in Table 1. As potential loss of sensory function can predispose patients with pDPN to adverse outcomes (e.g., skin lesions), sensory testing was performed. Most patients receiving HCCP or placebo either had no change (53–84% across tests) or improved values (12–30% across tests). Also, a 52-week open-label, randomized trial evaluating HCCP repeated treatment compared with standard of care in pDPN, reported no worsening in sensory perception of various stimuli with HCCP [6]. The authors did note that, in these studies, skin biopsies were not assessed to determine alterations in small nerve fibers. However, skin biopsies were taken in other studies and showed a consistent pattern of nerve regeneration over time. Chiang et al. [7] reported that, in healthy volunteers, application of capsaicin resulted in reversible degeneration and reinnervation of the epidermis and dermis, whereas Anand et al. [8] suggested that HCCP may facilitate regeneration and restoration of sensory nerve fibers based on baseline and 3-month post-treatment biopsies in chemotherapy-induced neuropathy.

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It is important to provide readers with a balanced view of the different treatment options, even when they only assess the abstract. However, no mention was made in the abstract of the array of well-known adverse effects caused by oral pDPN treatments (as in Table 1), whereas the suggestion that capsaicin causes degeneration of small nerve fibers was prominent. This creates an unbalanced view of the benefit–risk profile of topical capsaicin treatment and suggests that HCCP causes permanent damage to small nerve fibers, which in our opinion is not supported by the data.

In Sect. 5.13.3, "Topical Treatment with Capsaicin", in contrast with similar sections covering oral treatments, there is no elaboration on the benefits of topical capsaicin and, more specifically, HCCP. Moreover, this section does not differentiate between HCCP and low-dose capsaicin creams, which might result in significant misperceptions. For example, the authors mentioned that the use of topical capsaicin is limited by the frequency of application (four times daily) without noting that HCCP is a single 30-min application for pDPN that may be repeated every 90 days, as warranted by the persistence or return of pain.

The evidence of efficacy with HCCP in pDPN is robust. Simpson et al. [5] showed that the average daily pain score from baseline to weeks 2–12 reduced significantly ($P = 0.018$) with HCCP compared with placebo (mean ± standard deviation 28.0 ± 27.3% vs. 21.0 ± 29.4%, respectively). Moreover, a greater mean percentage reduction in Brief Pain Inventory-Diabetic Neuropathy sleep interference numeric pain rating scale score was seen with HCCP versus placebo from baseline to weeks 2–12 ($P = 0.020$ for weeks 2–12). The authors concluded, "In patients with pDPN, capsaicin 8% patch treatment provided modest pain relief and sleep quality improvements versus a placebo patch, similar in magnitude to other treatments with known efficacy, but without systemic side effects or sensory deterioration".

In Sect. 5.15, the authors advocated individualized therapy for older adults. Most oral treatments are associated with adverse events affecting the central nervous system (Table 1), which are often detrimental in elderly patients. Local treatments such as HCCP are valid alternatives given that they are devoid of such side effects because of their limited systemic absorption. Moreover, as older patients are often poly-medicated, the risk of drug–drug interactions is increased with oral therapy, and this is largely avoided with topical treatments for the same reason.

In conclusion, we believe it is important for all currently available treatments to be presented fairly in a state-of-the-art summary of the treatment of pDPN so physicians can make informed decisions about the best treatment options for individual patients.

Compliance with Ethical Standards

Conflict of interest M. Eerdekens and M. Stupar are employees of Grünenthal GmbH, and L. Marcondes is employee of GRT US Holding.

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