Painful diabetic neuropathy is an extremely disabling condition that may be present in at least a fifth of diabetic patients [1]. The etiology of painful diabetic neuropathy is complex with peripheral somatic [2,3], autonomic [4] and central thalamic perfusion defects identified in these patients [5]. The characteristic symptoms include symmetrical paresthesia, dysesthesia, electric shock-like pains and allodynia in the feet with nocturnal exacerbation. The treatment of this condition has remained unsatisfactory with a ‘good’ response to conventional medication rated at between 30–50% pain relief [6]. There are many available treatments, all are at best moderately effective, and their use is limited by side effects. Currently, there are only two US FDA-approved treatments, duloxetine and pregabalin, based on proven efficacy in randomized placebo-controlled trials; however, neither are entirely effective, particularly as patients can have a poor response and/or tolerability to both medications [7]. Furthermore, recent studies of novel drugs in the treatment of painful diabetic neuropathy have dramatically failed [8,9], with active treatment being barely superior to placebo. Therefore, there is a need to establish potential new mechanisms and, hence, treatments for painful diabetic neuropathy. It is, therefore, intriguing that a recent study has shown elevated levels of methylglyoxal in diabetic patients with painful neuropathy, and has shown that it mediates its effects by depolarizing sensory neurons and inducing post-translational modification of the voltage-gated sodium channel Na\textsubscript{1.8}, which is associated with increased electrical excitability, facilitating firing of nociceptive neurons [10]. Gain-of-function variants of the sodium channel Na\textsubscript{1.7} and, more recently, Na\textsubscript{1.8} have been found in a significant proportion of patients with painful neuropathy [11]. While these observations are of potential relevance, translation to clinically effective therapies is likely to take several years.

Vitamin D deficiency is highly prevalent in diabetic populations [12] and those with deficiencies are likely to have common characteristics to those with painful diabetic neuropathy. Three recent studies have found an association between vitamin D deficiency and diabetic neuropathy [13–15]; however, all have failed to assess the differences between positive (hyperalgesia and allodynia) and negative (paresthesia and
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Treatment
Studies of the therapeutic use of vitamin D in patients with painful diabetic neuropathy are limited. Vitamin D is thought to exert an effect on the peripheral nerve through NGF [17,18] and calbindin-D (a calcium-binding protein in the peripheral axon) [19]. A recent study from a rodent neuropathic pain model has shown an antinociceptive effect of 1,25-dihydroxyvitamin D3 in a dose-dependent manner [20]. To date, we know of only two interventional studies. The first by Valensi et al., who assessed the effects of a topical compound (QR-333) containing quercetin (which has aldose reductase inhibitor effects), ascorbyl palmitate and vitamin D3 [21]. Although this study was a double-blind placebo-controlled trial, with three distinct compounds that may induce active effects, it is difficult to define the relative effectiveness of vitamin D3. The second study by Lee et al. showed that oral cholecalciferol resulted in an approximate 50% reduction in painful neuropathic symptoms; however, this study had neither a placebo group nor was it randomized, leaving it open to considerable bias [22]. Vitamin D supplementation has been used effectively to treat other conditions of pain, particularly in rheumatological conditions [23,24]. However, a Cochrane review by Straube et al. concluded that there was a poor evidence base for the use of vitamin D in chronic pain, because studies were of variable quality with variable outcomes due to methodological differences [25]. There is a significant need for novel medication in the treatment of painful diabetic neuropathy. Furthermore, there is a growing body of evidence that vitamin D deficiency may be related to diabetic neuropathy. A well-constructed controlled trial of vitamin D supplementation in painful diabetic neuropathy is required in order to truly assess the effectiveness of this treatment. While awaiting the results of such studies, our current replacement regimen consists of an initial bolus of 40,000 U of vitamin D3 daily with the evening meal for 21 days, followed by a long-term maintenance dose of 20,000–40,000 U once weekly.

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References
Vitamin D & painful diabetic neuropathy: missing link or innocent bystander?  


