Editorial

Diabetic Peripheral Neuropathy and Associated Pain: Emerging and Updated Research

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Diabetic peripheral neuropathy (DPN) is estimated to affect 30% to 50% of all adults with diabetes in the United States. Evidence suggests that poor glycemic control and duration of diabetes along with components of metabolic syndrome, including dyslipidemia, obesity, and hypertension, may affect the prevalence of DPN.[1] DPN is associated with increased risk of falls among older patients with type 2 diabetes, and poorly managed DPN can lead to lower limb amputation.[2] The ideal is to screen for limited sensation and onset of neuropathy using inexpensive tools, including the 10-g Semmes-Weinstein monofilament examination, superficial pain sensation, and vibration testing by the on-off method; however, evidence suggests that, for a variety of systems-oriented reasons, screening is not performed in some health care systems and no treatment of any kind is offered.[3] Instead, patients are diagnosed with DPN based on patient symptoms of pain and discomfort, and they are treated for their pain. A 2001 report suggested that the likelihood of neuropathy may be easily and inexpensively predicted using the reported operating characteristics for each of these 3 tests, whereas the fourth test, vibration testing using the timed method, introduces some minor complications and extra time.[4] There is no cure for neuropathy; however, the pain and discomfort may be managed and lessened with pharmacotherapy and durable equipment. A recent systematic review found evidence that neuropathy-related pain reduction may be achieved using the serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine, the anticonvulsants pregabalin and oxcarbazepine, tricyclic antidepressants, atypical opioids, and botulinum toxin.[5]

Failure to address the pain and discomfort from neuropathy early during the progression of the condition places the patient at risk for falls and subsequent injuries. Many patients experience proximal neuropathy (eg, pain in the thighs, hips, or buttocks), whereas others experience focal neuropathy, resulting in the sudden weakness of one nerve or a group of nerves, causing muscle weakness or pain. The prevalence of diagnosed DPN is higher among patients who are black (22%) and Hispanic (25%) compared with white patients with type 2 diabetes.[6] Furthermore, racial and ethnic minorities may be at increased risk because of underreporting of symptoms and underdiagnosis of chronic pain conditions linked to DPN, particularly when culture, language, and other communication barriers are present.[7]

Despite this rather bleak outlook for patients with neuropathy, the current issue of *Clinical Therapeutics* features research that suggests that there may be optimism regarding reducing neuropathic pain. A review by Parasoglou and Rao[8] of New York University entitled, "Declining Skeletal Muscle Function in Diabetic Peripheral Neuropathy," offers an update on the most recent trials of exercise interventions that target DPN and promising magnetic resonance imaging techniques that are providing a foundation for future clinical trials. We also include a review article entitled, "Efficacy of Venlafaxine in Neuropathic Pain: A Narrative Review Towards Optimized

Treatment," by Trouvin and colleagues[9] from Hopital Cochin, Paris, that addresses the effectiveness of venlafaxine for neuropathic pain. Hidmark and colleagues,[10] based at the Universitat Heidelberg, described the effect of external electric muscle stimulation in reducing neuropathic pain, in their article, "Electrical Muscle Stimulation Induces an Increase of VEGFR2 on Circulating Hematopoietic Stem Cells in Diabetes Patients."

Aside from the neuropathic pain that presents in advanced diabetes, an important outcome of type 2 diabetes is the substantially increased risk of cardiovascular (CV) disease.[11] As reported in a previous editorial[12] and a review of the CV effects of glucose-lowering therapies[13] published in *Clinical Therapeutics* in conjunction with the American Heart Association's 2016 Scientific Sessions, several drugs in the sodium/glucose cotransporter 2 (SGLT-2) and glucagon-like peptide *1* classes have good evidence of CV risk reduction.

The SGLT-2 class has been suggested to reduce CV risk factors by affecting blood pressure, weight, visceral adiposity, hyperinsulinemia, arterial stiffness, albuminuria, circulating uric levels, and oxidative stress.[14] Several outcome trials have been launched since the major regulatory agencies introduced their requirements that new type 2 diabetes compounds be evaluated to understand effect on CV risk.[15,16] These trials include the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG Outcome),[17] Canagliflozin Cardiovascular Assessment Study (CANVAS),[18] Canagliflozin Cardiovascular Assessment Study: A Study of the Effects of Canagliflozin in Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus (CANVAS-R),[19] Canagliflozin and Renal Events in Diabetes with an Established Nephropathy Clinical Evaluation Study (CREDENCE),[14] Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58),[14] and Ertugliflozin Cardiovascular Outcome Trial.[14] Of these, results from the EMPA-REG Outcome trial were reported in 2015,[20] whereas various preliminary analyses of CANVAS data have also been published before the final CANVAS trial results, expected in 2017 to 2018, including 2 previous reports in *Clinical Therapeutics*.[21,22] The CV implications of SGLT-2 medications will continue to be reported as analyses of these outcome trials are completed between 2017 and 2021. Meanwhile, we include a third preliminary study of canagliflozin in this month's issue of *Clinical Therapeutics* in which electronic medical record data, reflecting real-world evidence, are used for a subgroup analysis of the glycemic outcomes of canagliflozin.[23]

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