DM, mimic diabetic neuropathy, and may be treatable.[547] Thus, undertaking a thorough family and medication history and performing relevant investigations are helpful to assess other potential etiologies, such as alcohol abuse, genetic neuropathies, neoplasia, toxic exposure, and amyloidosis. Laboratory screening includes vitamin B_{12} levels to test for B_{12} deficiency (particularly in persons treated with metformin), thyroid function tests, complete blood count, metabolic panel, and serum immunoelectrophoresis with immunofixation to test for a monoclonal gammopathy.[547]

As recommended by the Toronto Consensus on Diabetic Neuropathy,[568] for research purposes, a diagnosis of confirmed diabetic neuropathy requires a combination of symptoms, signs, and abnormality of objective tests such as changes in nerve conduction studies. The symptoms and signs of DPN have been broadly covered above in the clinical section. However, for research, a range of assessments, including more objective measures and importantly, person-reported outcomes, has been developed over time and validated. The use of validated clinical instruments such as the Michigan Neuropathy Screening Instrument (most widely used in large cohorts of persons with T1D and T2D),[69,417,546,550,569-571] the modified Toronto Clinical Neuropathy Scale,[572] the Utah Early Neuropathy Scale,[573] or the Neuropathy Disability Score[574] are feasible and can be done in a standardized fashion in large cohorts of persons with DM. Instruments for painful DPN also have been validated.[556,558]

In addition to screening for DPN, a comprehensive foot examination at all outpatient office visits is necessary to identify foot ulcerations, infections, vascular insufficiency, and deformities that could lead to limb loss or mortality.[575] The global burden of foot complications, including ulcerations, infections, and ischemia that may lead to amputation, is between 2.2% to 6.3% of persons with DM per year, and the lifetime risk of any foot complication is up to 34% in persons with DM.[576,577] Recurrence of foot ulcerations after healing is common, up to 50% at 3 years.[576] Most foot ulcerations have a neuropathic component[577] and are preventable by foot care that includes daily inspection, nail and skin care, correction of foot deformities, and/or provision of appropriate footwear to accommodate structural changes.[578] In-office examination should include inspection for vascular insufficiency, musculoskeletal deformities, skin breakdown, or abnormal skin callus formation in addition to the DPN examination.[579] Referral to podiatry or others on a multispecialty team may prevent infections and ulcerations from progressing to limb loss.[580] Risk assessment for diabetic foot problems is integral to comprehensive care of persons with DM.[575]

Prevention of Diabetic Peripheral Neuropathy

Prevention of diabetic neuropathies focuses on glucose control and lifestyle modifications. Enhanced glucose control in people with T1D dramatically reduces the incidence of DPN (78% relative risk reduction),[78,542,547,549] and glucose control remains the strongest risk factor for DPN in T1D even in contemporary cohorts.[417,542-544,547] Despite socioeconomic barriers being associated with DPN, one should aim to achieve near-normal glycemia in persons with T1D at risk of DPN.[544] In contrast, enhanced glucose control in people with T2D reduces the risk of developing DPN more modestly.[547,557] The ACCORD trial in individuals with T2D reported a modest but significant DPN risk reduction with intensive glycemia intervention after 5 years of follow-up,[69] but other trials reported inconclusive effects.[547] Specific glucose-lowering strategies may contribute to the discrepancy. For example, participants, particularly men, in the BARI 2D trial treated with insulin sensitizers had a lower incidence of DPN over 4 years than those treated with insulin/SUs.[570] There is also emerging evidence that lifestyle modifications either as exercise alone (supervised aerobic with or without resistance training), combined dietary modification and exercise, or other behavioral interventions may have beneficial effects on preventing DPN in some persons with T2D or prediabetes.[547,526,582,583,581-586] Emerging evidence shows a potential benefit of bariatric surgery on reducing risk of DPN.[587]

Management of Diabetic Peripheral Neuropathy

Despite major advances in elucidating the pathogenesis of diabetic neuropathy, there remains a lack of disease-modifying treatment options in individuals with DM; hence, there is an urgent need for more targeted research.

Currently, there is no convincing evidence supporting glucose control or lifestyle management as therapies for neuropathic pain in DM or prediabetes. At present, among pharmacological options, pregabalin[588-598] and duloxetine[594,595,599,600] are oral agents that have received regulatory approval for the treatment of neuropathic pain associated with DPN by the FDA and are effective for DPN pain reduction when using patient-reported outcomes.[547] In addition, based on evidence from 2 large 12-week randomized multicenter trials in 2020, the FDA approved the cutaneous concentrated capsaicin 8% patch that works by desensitizing and interfering with the function of the transient receptor potential vanilloid 1 receptor, a protein involved in pain signaling. However, the patch needs to be applied for ~30 minutes and can be done only in the office with a physician present.[601,602] The opioid, tapentadol, has received regulatory approval in the United States and Canada, but evidence for its use is, at best, inconclusive,[603,604] and the ADA and other organizations strongly recommend against using any opioids for management of DPN pain.[547] Reviewing evidence for the variety of agents that can modify DPN pain, one should use a stepwise approach and consider an individual's comorbidities, socioeconomic status, and potential drug interactions.[547,605] Nonsteroidal anti-inflammatory agents should be avoided for chronic pain management in persons with DM due to adverse kidney effects. Given the high risk of addiction, abuse, sedation, and other complications and psychosocial issues, even with short-term opioid use, opioids are not recommended in the treatment of painful DPN.[547] High frequency (eg,10 kHz) spinal cord stimulation is a nonpharmacological approach that may be effective in persons with painful DPN that failed at least one medication, as suggested by a recent large RCT, leading to FDA approval in 2021 (Fig. 4).[606,607]

Regular aerobic, strengthening, and balance exercise, alone or in combination; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats have all demonstrated positive outcomes for individuals with DPN, including for neuropathic pain reduction.[581-583,586,608-610] Small-fiber neuropathies should be managed with foot protection (eg, padded socks); supportive shoes with orthotics, if necessary; regular foot and shoe inspection; prevention of heat injury; and use of emollient creams.[547] Regular foot and nail care by a trained professional is recommended. Advanced stages of large-fiber neuropathies may require a multidisciplinary approach to include strategies to enhance muscle strength, gait, and balance training; titrate any pain or other medications that could promote dizziness and other side effects affecting gait and balance; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction in case of deformities.[547,609]

Autonomic Neuropathies

Autonomic neuropathies affect the autonomic neurons (parasympathetic, sympathetic, or both) and are associated with a variety of condition-specific symptoms and signs that should be evaluated during the medical history and physical examination of all individuals with DM.[547] CAN is the most studied and clinically relevant of the diabetic autonomic neuropathies, whereas GI, genitourinary, and sudomotor dysfunction may also develop during