



12. Retinopathy, Neuropathy, and Foot Care: *Standards of Medical Care in Diabetes—2022*

American Diabetes Association
Professional Practice Committee*

Diabetes Care 2022;45:S185–S194 | <https://doi.org/10.2337/dc22-S012>

The American Diabetes Association (ADA) “Standards of Medical Care in Diabetes” includes the ADA’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (<https://doi.org/10.2337/dc22-SPPC>), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA’s clinical practice recommendations, please refer to the Standards of Care Introduction (<https://doi.org/10.2337/dc22-SINT>). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, “Children and Adolescents” (<https://doi.org/10.2337/dc22-S014>).

DIABETIC RETINOPATHY

Recommendations

- 12.1 Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- 12.2 Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve patient reported visual function (2,7–10). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor

*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at <https://doi.org/10.2337/dc22-SPPC>.

Suggested citation: American Diabetes Association Professional Practice Committee. 12. Retinopathy, neuropathy, and foot care: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022; 45(Suppl. 1):S185–S194

© 2021 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://diabetesjournals.org/journals/pages/license>.

agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic control on retinopathy was not studied in these trials. Retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RAs (11).

Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor or retinopathy severity is advanced at the time of conception (12,13). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for patients with high-risk proliferative diabetic retinopathy (PDR) or center-involved diabetic macular edema (13). Anti-vascular endothelial growth factor (anti-VEGF) medications should not be used in pregnant patients with diabetes because of theoretical risks to the vasculature of the developing fetus.

Screening

Recommendations

- 12.3** Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- 12.4** Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- 12.5** If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- 12.6** Programs that use retinal photography (with remote reading

or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

- 12.7** Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- 12.8** Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy. Prompt diagnosis allows triage of patients and timely intervention that may prevent vision loss in patients who are asymptomatic despite advanced diabetic eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (14) (see Section 14, “Children and Adolescents,” <https://doi.org/10.2337/dc22-S014>). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-controlled type 2 diabetes, there was little risk of development of significant retinopathy with a 3-year interval after a normal examination (15), and less frequent intervals have been found in simulated modeling to be

potentially effective in screening for diabetic retinopathy in patients without diabetic retinopathy (16). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as uncontrolled hyperglycemia or advanced baseline retinopathy or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (17–19). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (17,20,21). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema, authorized for use by the U.S. Food and Drug Administration (FDA), represent an alternative to traditional screening approaches (22). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (23).

Type 2 Diabetes

Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent

diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Pregnancy is associated with a rapid progression of diabetic retinopathy (24,25). Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (13). Women who develop gestational diabetes mellitus do not require eye examinations during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (26).

Treatment

Recommendations

- 12.9** Promptly refer patients with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**
- 12.10** Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**
- 12.11** Intravitreal injections of anti-vascular endothelial growth factor are a reasonable alternative to traditional panretinal laser photocoagulation for some patients with proliferative diabetic retinopathy and also reduce the risk of vision loss in these patients. **A**
- 12.12** Intravitreal injections of anti-vascular endothelial growth factor are indicated as first-line treatment for most eyes with

diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-vascular endothelial growth factor therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (27) showed in 1978 that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). In 1985, the ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications. A more gentle, macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (28), but this is now largely considered to be second-line treatment for diabetic macular edema.

Anti-Vascular Endothelial Growth Factor Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to non-inferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (29,30). In addition, it was observed that patients treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema. However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some patients. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema but has not been shown to improve visual outcomes over 2 years of therapy and therefore is not routinely recommended for this indication (31).

While the ETDRS (28) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment regimen for center-involved diabetic macular edema than monotherapy with laser (32,33). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema. There are currently three anti-VEGF agents commonly

used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (1)—and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (34). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides similar 2-year vision outcomes compared with immediate initiation of anti-VEGF therapy (35).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids. Both of these therapies are also reasonable first-line approaches for patients who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (8). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (36,37).

NEUROPATHY

Screening

Recommendations

12.15 All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.16 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament

testing to identify feet at risk for ulceration and amputation. **B**

12.17 Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important.

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (38,39) and may modestly slow their progression in type 2 diabetes (40), but it does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (41) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (41). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers

may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: vibration perception and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (42). See the American Diabetes Association position statement “Diabetic Neuropathy” for more details (41).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Cardiac Autonomic Neuropathy. CAN is associated with mortality independently of other cardiovascular risk factors (43,44). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic

blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies. Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ¹³C octanoic acid breath test is emerging as a viable alternative.

Genitourinary Disturbances. Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (41). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (45). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.18 Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **A** and to slow the progression

of neuropathy in patients with type 2 diabetes. **B**

12.19 Assess and treat patients to reduce pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**

12.20 Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in patients with type 1 diabetes (46–49). Although the evidence for the benefit of near-normal glycemic control is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (40,50). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (51).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (52). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (53).

Pregabalin and duloxetine have received regulatory approval by the FDA, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes. The opioid tapentadol has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (54). Comparative effectiveness studies and trials that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often

follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacologic strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (55–57).

Pregabalin, a calcium channel $\alpha 2\text{-}\delta$ subunit ligand, is the most extensively studied drug for DPN. The majority of studies testing pregabalin have reported favorable effects on the proportion of participants with at least 30–50% improvement in pain (54,56, 58–61). However, not all trials with pregabalin have been positive (54,56,62,63), especially when treating patients with advanced refractory DPN (60). Adverse effects may be more severe in older patients (64) and may be attenuated by lower starting doses and more gradual titration. The related drug, *gabapentin*, has also shown efficacy for pain control in diabetic neuropathy and may be less expensive, although it is not FDA approved for this indication (65).

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DPN in multicenter randomized trials, although some of these had high dropout rates (54,56,61,63). Duloxetine also appeared to improve neuropathy-related quality of life (66). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (67). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol is a centrally acting opioid analgesic that exerts its analgesic effects through both μ -opioid receptor agonism and noradrenergic reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials in which participants titrated to an optimal dose of tapentadol were randomly assigned to continue that dose or switch to placebo (68,69). However, both used a design enriched for patients who responded to tapentadol, and therefore their results are not generalizable. A recent systematic review and meta-analysis by the Special Interest Group on

Neuropathic Pain of the International Association for the Study of Pain found the evidence supporting the effectiveness of tapentadol in reducing neuropathic pain to be inconclusive (54). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of extended-release tapentadol is not generally recommended as a first- or second-line therapy. The use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (41,54,56).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these patients, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β -blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if patients are unable to tolerate preferred agents (70–72). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (73–75). In

addition, foods with small particle size may improve key symptoms (76). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (73,77). In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA or the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (77). Other treatment options include domperidone (available outside of the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (78,79). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to patients with severe symptoms that are refractory to other treatments (80).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intra-urethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve the patient's quality of life.

FOOT CARE

Recommendations

- 12.21** Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- 12.22** Patients with evidence of sensory loss or prior ulceration or amputation should have

their feet inspected at every visit. **B**

- 12.23** Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**

- 12.24** The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment, including pulses in the legs and feet. **B**

- 12.25** Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **C**

- 12.26** A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot or prior ulcers or amputation). **B**

- 12.27** Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and life-long surveillance. **C**

- 12.28** Provide general preventive foot self-care education to all patients with diabetes. **B**

- 12.29** The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes, including those with severe neuropathy, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

Foot ulcers and amputation, which are consequences of diabetic neuropathy

and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with diabetes.

Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Poor glycemic control
- Peripheral neuropathy with LOPS
- Cigarette smoking
- Foot deformities
- Preulcerative callus or corn
- PAD
- History of foot ulcer
- Amputation
- Visual impairment
- Chronic kidney disease (especially patients on dialysis)

Moreover, there is good-quality evidence to support use of appropriate therapeutic footwear with demonstrated pressure relief that is worn by the patient to prevent plantar foot ulcer recurrence or worsening. However, there is very little evidence for the use of interventions to prevent a first foot ulcer or heal ischemic, infected, non-plantar, or proximal foot ulcers (81). Studies on specific types of footwear demonstrated that shape and barefoot plantar pressure-based orthoses were more effective in reducing submetatarsal head plantar ulcer recurrence than current standard-of-care orthoses (82).

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (83).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually. Detailed foot assessments may occur more frequently in patients with histories of ulcers or amputations, foot deformities, insensate feet, and PAD (84,85). To assess risk, clinicians should ask about history of foot ulcers or amputation, neuropathic and peripheral vascular symptoms, impaired vision, renal disease, tobacco use, and foot care

practices. A general inspection of skin integrity and musculoskeletal deformities should be performed. Vascular assessment should include inspection and palpation of pedal pulses.

The neurological exam performed as part of the foot examination is designed to identify LOPS rather than early neuropathy. The 10-g monofilament is the most useful test to diagnose LOPS. Ideally, the 10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration sensation using a 128-Hz tuning fork, or ankle reflexes). Absent monofilament sensation suggests LOPS, while at least two normal tests (and no abnormal test) rules out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of decreased walking speed, leg fatigue, claudication, and an assessment of the pedal pulses. Ankle-brachial index testing should be performed in patients with symptoms or signs of PAD. Additionally, at least one of the following tests in a patient with a diabetic foot ulcer and PAD should be performed: skin perfusion pressure (≥ 40 mmHg), toe pressure (≥ 30 mmHg), or transcutaneous oxygen pressure ($TcPO_2 \geq 25$ mmHg). Urgent vascular imaging and revascularization should be considered in a patient with a diabetic foot ulcer and an ankle pressure (ankle-brachial index) < 50 mmHg, toe pressure < 30 mmHg, or a $TcPO_2 < 25$ mmHg (41,86).

Patient Education

All patients with diabetes and particularly those with high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) and their families should be provided general education about risk factors and appropriate management (87). Patients at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot monitoring on a daily basis. Patients with LOPS should be educated on ways to substitute other sensory modalities (palpation or visual inspection using an unbreakable mirror) for surveillance of early foot problems.

The selection of appropriate footwear and footwear behaviors at home should also be discussed. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

Treatment

People with neuropathy or evidence of increased plantar pressures (e.g., erythema, warmth, or calluses) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra wide or deep shoes. People with bony deformities, including Charcot foot, who cannot be accommodated with commercial therapeutic footwear, will require custom-molded shoes. Special consideration and a thorough workup should be performed when patients with neuropathy present with the acute onset of a red, hot, swollen foot or ankle, and Charcot neuroarthropathy should be excluded. Early diagnosis and treatment of Charcot neuroarthropathy is the best way to prevent deformities that increase the risk of ulceration and amputation. The routine prescription of therapeutic footwear is not generally recommended. However, patients should be provided adequate information to aid in selection of appropriate footwear. General footwear recommendations include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole. Use of custom therapeutic footwear can help reduce the risk of future foot ulcers in high-risk patients (84,87).

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. Staphylococci and streptococci are the most common causative organisms. Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at gram-positive cocci in many patients

with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (88). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes (88).

Hyperbaric oxygen therapy (HBOT) in patients with diabetic foot ulcers has mixed evidence supporting its use as an adjunctive treatment to enhance wound healing and prevent amputation (89–92). A well-conducted randomized controlled study performed in 103 patients found that HBOT did not reduce the indication for amputation or facilitate wound healing compared with comprehensive wound care in patients with chronic diabetic foot ulcers (93). Moreover, a systematic review by the International Working Group on the Diabetic Foot of interventions to improve the healing of chronic diabetic foot ulcers concluded that analysis of the evidence continues to present methodological challenges as randomized controlled studies remain few, with a majority being of poor quality (90). Thus, HBOT does not have a significant effect on health-related quality of life in patients with diabetic foot ulcers (94,95). A recent review concluded that the evidence to date remains inconclusive regarding the clinical and cost-effectiveness of HBOT as an adjunctive treatment to standard wound care for diabetic foot ulcers (96). Results from the Dutch DAMOCLES (Does Applying More Oxygen Cure Lower Extremity Sores?) trial demonstrated that HBOT in patients with diabetes and ischemic wounds did not significantly improve complete wound healing and limb salvage (97). While the Centers for Medicare & Medicaid Services currently covers HBOT for diabetic foot ulcers that have failed a standard course of wound therapy when there are no measurable signs of healing for at least 30 consecutive days (98), given the data not supporting an effect, such an approach is not currently warranted. HBOT should be a topic of shared decision-making before treatment is considered for selected patients with diabetic foot ulcers (98).

References

- Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:412–418
- Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
- Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia* 2001;44:156–163
- Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 1998;31:947–953
- Yau JWY, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–564
- Eid S, Sas KM, Abcouwer SF, et al. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019;62:1539–1549
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
- Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
- Writing Team for the DCCT/EDIC Research Group; Gubitosi-Klug RA, Sun W, Cleary PA, et al. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. *JAMA Ophthalmol* 2016;134:137–145
- Aiello LP, Sun W, Das A, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med* 2015;372:1722–1733
- Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA_{1c} change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. *Diabetes Care* 2021;44:290–296
- Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004;27:2540–2553
- Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care* 2000;23:1084–1091
- Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA* 2017;317:825–835
- Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011;34:1318–1319
- Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med* 2017;376:1507–1516
- Silva PS, Horton MB, Clary D, et al. Identification of diabetic retinopathy and ungradable image rate with ultrawide field imaging in a national teleophthalmology program. *Ophthalmology* 2016;123:1360–1367
- Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol* 2011;129:435–444
- Walton OB 4th, Garoon RB, Weng CY, et al. Evaluation of automated teleretinal screening program for diabetic retinopathy. *JAMA Ophthalmol* 2016;134:204–209
- Daskivich LP, Vasquez C, Martinez C Jr, Tseng C-H, Mangione CM. Implementation and evaluation of a large-scale teleretinal diabetic retinopathy screening program in the Los Angeles County Department of Health Services. *JAMA Intern Med* 2017;177:642–649
- Sim DA, Mistry D, Alexander P, et al. The evolution of teleophthalmology programs in the United Kingdom: beyond diabetic retinopathy screening. *J Diabetes Sci Technol* 2016;10:308–317
- Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *npj Digit Med* 2018;1:39
- Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol* 2012;47(Suppl.):S1–S30
- Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. *Ophthalmology* 1996;103:1815–1819
- Best RM, Chakravarthy U. Diabetic retinopathy in pregnancy. *Br J Ophthalmol* 1997;81:249–251
- Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetes* 2007;56:2990–2996
- The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–396
- Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–1806
- Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreal ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015;314:2137–2146
- Sivaprasad S, Prevost AT, Vasconcelos JC, et al.; CLARITY Study Group. Clinical efficacy of

- intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet* 2017;389:2193–2203
31. Maturi RK, Glassman AR, Josic K, et al.; DRCR Retina Network. Effect of intravitreal anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol* 2021;139:701–712
32. Elman MJ, Bressler NM, Qin H, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609–614
33. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–625
34. Wells JA, Glassman AR, Ayala AR, et al.; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193–1203
35. Baker CW, Glassman AR, Beaulieu WT, et al.; DRCR Retina Network. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA* 2019;321:1880–1894
36. Chew EY, Davis MD, Danis RP, et al.; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study. *Ophthalmology* 2014;121:2443–2451
37. Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a meta-analysis and systematic review. *Int J Ophthalmol* 2018;11:287–295
38. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014;14:528
39. Martin CL, Albers JW; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:31–38
40. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
41. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136–154
42. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
43. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
44. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). *J Am Coll Cardiol* 2013;61:447–454
45. Smith AG, Lessard M, Reyna S, Doudova M, Singleton JR. The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. *J Diabetes Complications* 2014;28:511–516
46. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 1995;38:869–880
47. CDC Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416–423
48. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. *Diabetes Care* 2010;33:1090–1096
49. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation* 2009;119:2886–2893
50. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
51. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. *Diabetes Care* 2013;36:3208–3215
52. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. *Diabetes Metab Syndr Obes* 2013;6:79–92
53. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. *Neurology* 2017;88:1958–1967
54. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–173
55. Brill V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in *Neurology* 2011;77:603]. *Neurology* 2011;76:1758–1765
56. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med* 2014;161:639–649
57. Ziegler D, Fonseca V. From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy. *J Diabetes Complications* 2015;29:146–156
58. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008;31:1448–1454
59. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009;3:CD007076
60. Raskin P, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. *Clin J Pain* 2014;30:379–390
61. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The “COMBO-DN study”—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013;154:2616–2625
62. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. *Pain* 2015;156:2013–2020
63. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol* 2009;9:6
64. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* 2007;8:118–126
65. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2017;6:CD007938
66. Wernicke JF, Pritchett YL, D’Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006;67:1411–1420
67. Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJM. Does treatment with duloxetine for neuropathic pain impact glycemic control? *Diabetes Care* 2007;30:21–26
68. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011;27:151–162
69. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of

- tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care* 2014;37:2302–2309
70. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. *J Clin Hypertens (Greenwich)* 2014;16:141–148
71. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. *Cleve Clin J Med* 2010;77:298–306
72. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. *J Hypertens* 2019;37:1541–1546
73. Camilleri M, Parkman HP, Shafi MA, Abell TL; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18–37; quiz 38
74. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. *Diabetes Spectr* 2007;20:231–234
75. Parkman HP, Yates KP, Hasler WL, et al.; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* 2011;141:486–498, 498.e1–498.e7
76. Olausson EA, Störsrud S, Grundin H, Isaksson M, Attvall S, Simrén M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol* 2014;109:375–385
77. Umpierrez GE, Ed. *Therapy for Diabetes Mellitus and Related Disorders*. 6th ed. Alexandria, VA, American Diabetes Association, 2014
78. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. *Clin Gastroenterol Hepatol* 2008;6:726–733
79. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263
80. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. *Clin Gastroenterol Hepatol* 2010;8:947–954; quiz e116
81. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF; International Working Group on the Diabetic Foot. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):99–118
82. Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. *Diabetes Care* 2014;37:1982–1989
83. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679–1685
84. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg* 2016;63(Suppl.):35–215
85. Litzelman DK, Slemenda CW, Langefeld CD, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 1993;119:36–41
86. International Working Group on the Diabetic Foot. IWGDF guidelines on the prevention and management of diabetic foot disease. IWGDF Guidelines, 2019. Accessed 12 October 2021. Available from <https://iwgdfguidelines.org/wp-content/uploads/2019/05/IWGDF-Guidelines-2019.pdf>
87. Bonner T, Foster M, Spears-Lanoix E. Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the United States: a systematic review of the literature. *Diabet Foot Ankle* 2016;7:29758
88. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012;54:e132–e173
89. Elraiyah T, Tsapas A, Prutsky G, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. *J Vasc Surg* 2016;63(Suppl):465–585.E2
90. Game FL, Apelqvist J, Attinger C, et al.; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):154–168
91. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;6:CD004123
92. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;33:998–1003
93. Fedorko L, Bowen JM, Jones W, et al. hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. *Diabetes Care* 2016;39:392–399
94. Li G, Hopkins RB, Levine MAH, et al. Relationship between hyperbaric oxygen therapy and quality of life in participants with chronic diabetic foot ulcers: data from a randomized controlled trial. *Acta Diabetol* 2017;54:823–831
95. Boulton AJM, Whitehouse RW. The diabetic foot. In *Endotext*. Feingold KR, Anawalt B, Boyce A, et al., Eds. South Dartmouth, MA, MDText.com, Inc., 2000–2021. Accessed 12 October 2021. Available from <https://www.ncbi.nlm.nih.gov/books/NBK409609/>
96. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. *Ont Health Technol Assess Ser* 2017;17:1–142
97. Stoekenbroek RM, Santema TB, Koelemay MJ, et al. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial? *J Diabetes* 2015;7:125–132
98. Huang ET, Mansouri J, Murad MH, et al.; UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. *Undersea Hyperb Med* 2015;42:205–247