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Diabetic Peripheral Neuropathy: Diagnosis and Management CME/CE

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Vivian A. Fonseca, MD

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Target Audience

This activity is intended for endocrinologists, diabetologists, podiatrists, primary care providers, and nurses who provide care for patients with type 2 diabetes.

Goal

The goals of this activity are to describe the clinical presentation of diabetic peripheral neuropathy (DPN); discuss available assessment, evaluation, and screening tools; and describe the role of current and novel treatment options.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Discuss the clinical importance of regular physical examinations and screening for DPN in patients with type 2 diabetes
2. Identify available screening, assessment, and evaluation tools for diagnosing DPN
3. Describe the importance of glycemic control and the role of current and novel approaches to the management of DPN

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Disclosure: Vivian A. Fonseca, MD, has disclosed the following relevant financial relationships:
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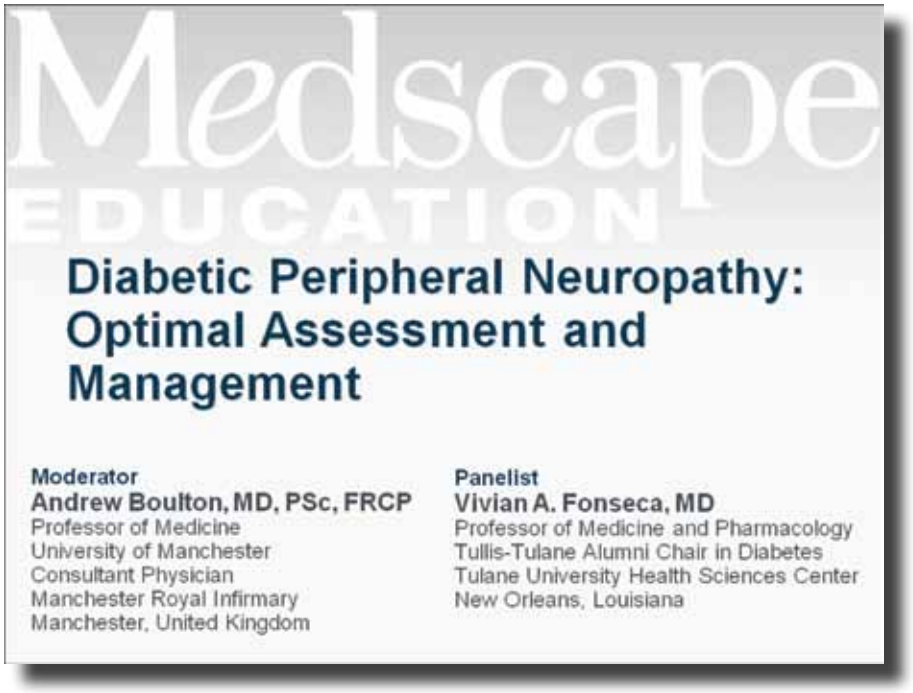
Diabetic Peripheral Neuropathy: Optimal Assessment and Management CME/CE

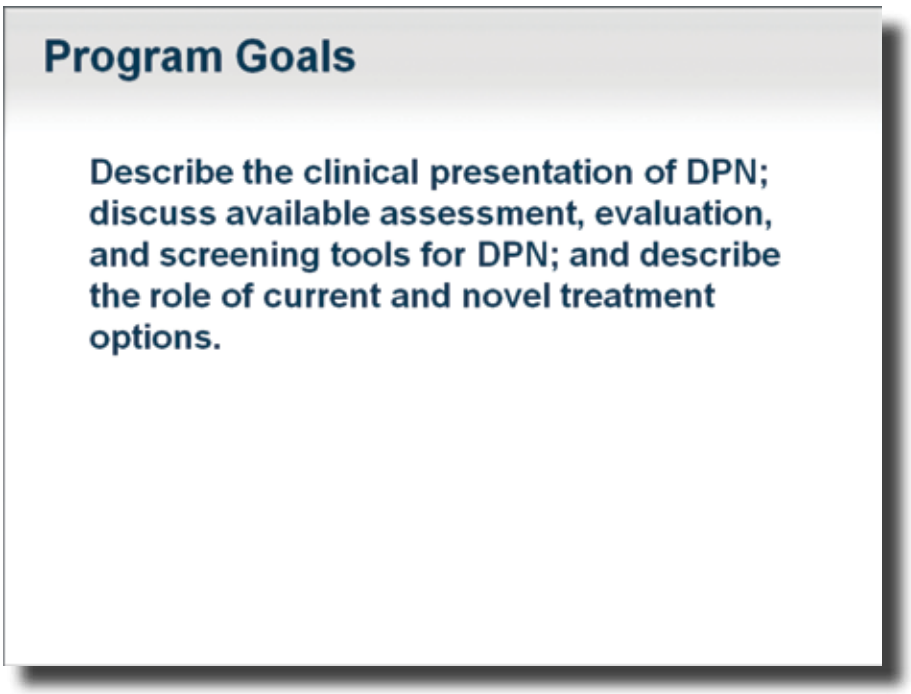
Welcome and Introduction



Slide 1.

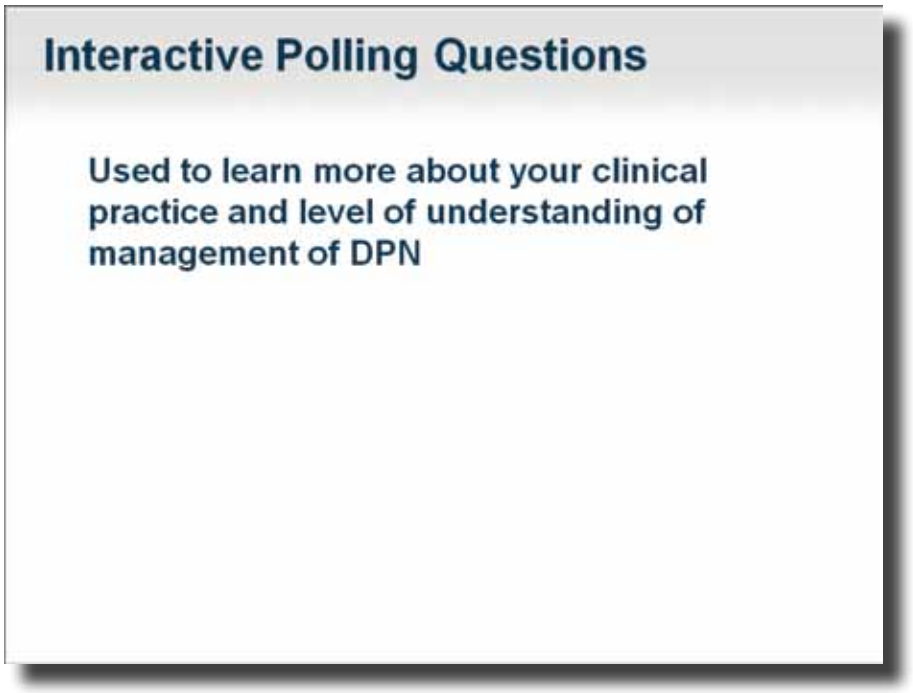
Andrew Boulton, MD: Hello and welcome to this discussion Diabetic Peripheral Neuropathy: Optimal Assessment and Management. My name is Dr. Andrew Boulton and I'm a Professor of Medicine at the University of Manchester and Consultant Physician in Manchester Royal Infirmary in the United Kingdom. I am also a visiting professor at the University of Miami in Florida. It is a pleasure for me to introduce Dr. Vivian Fonseca, a Professor of Medicine and Pharmacology at the Tulane University Medical Sciences Center in New Orleans, Louisiana. Welcome, Vivian, to our discussion.

Vivian A. Fonseca, MD: Thank you.



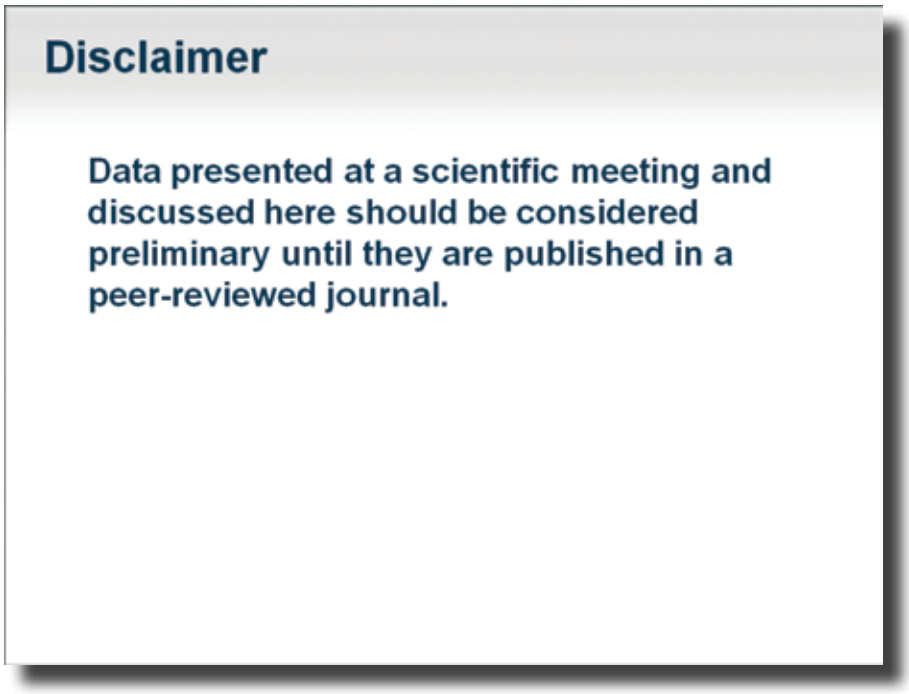
Slide 2.

Dr. Boulton: The goals of today's discussion are to better understand the clinical presentation of diabetic peripheral neuropathy, or DPN, and to discuss available assessment, evaluation, and screening tools and the role of current and novel treatment options.



Slide 3.

We will be using interactive polling questions to learn more about your clinical practice and your level of understanding of DPN.



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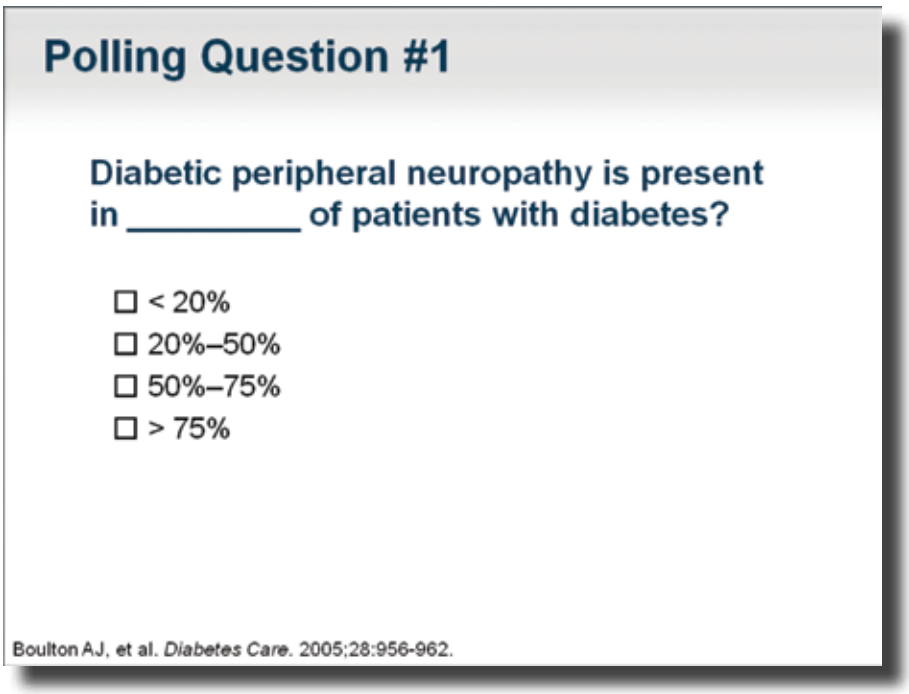
This activity will include expert perspectives on studies published in abstract form and presented at a scientific congress. These data should be considered as preliminary until they are published in a peer-reviewed journal.



Slide 5.

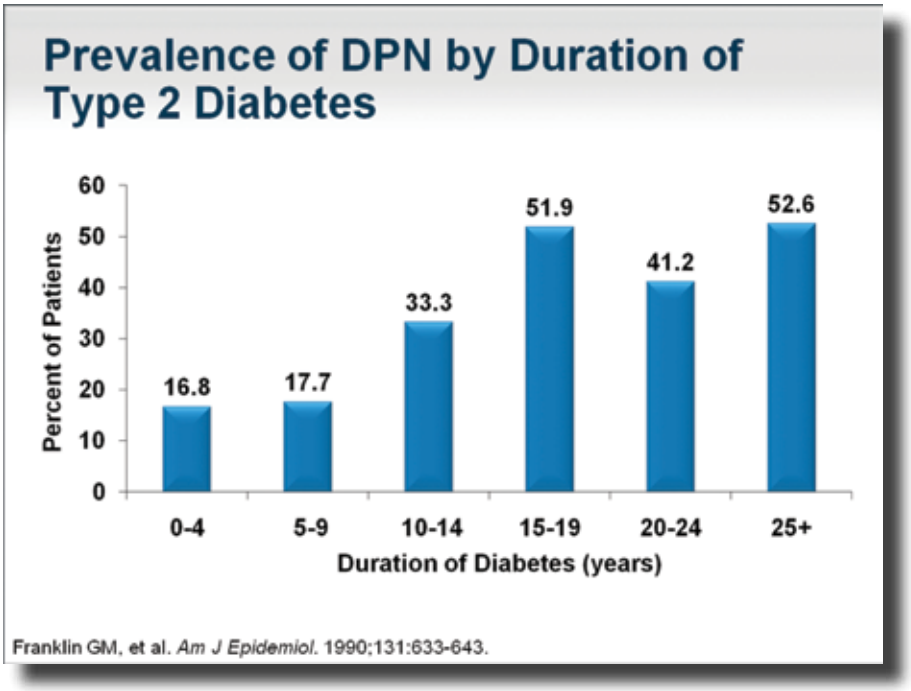
Let's ask our first polling question. How would you answer this statement?

Diabetic peripheral neuropathy is present in what percentage of your patients with diabetes?

- < 20%
- 20%-50%
- 50%-75%
- > 75%

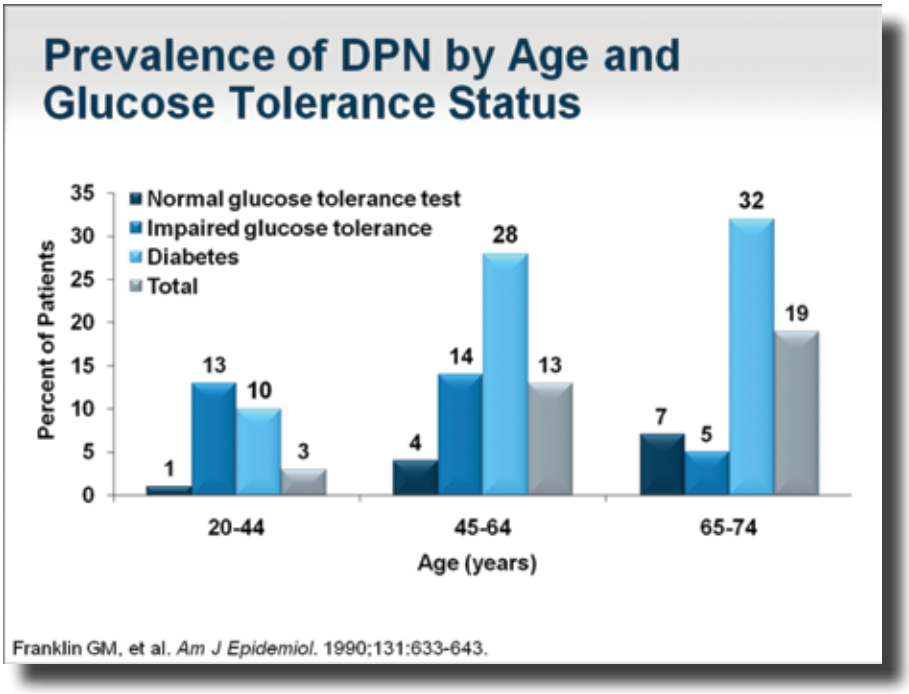
Prevalence and Definition of DPN

Dr. Fonseca, how often will neuropathy occur in your patients with type 2 diabetes?



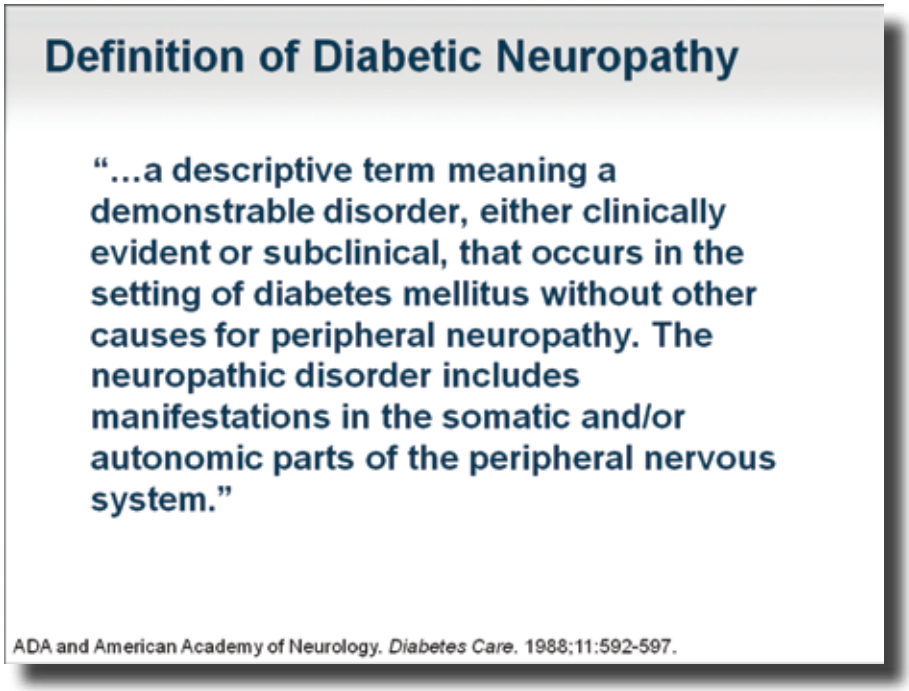
Slide 6.

Dr. Fonseca: This is a very interesting question. It depends on what population you look at, how you examine them, and how you assess neuropathy. A number of tools, which we will discuss later, are used to make a diagnosis and depending on which one you use, you have different [diagnosis rates], but in general, it is thought that after about 15-20 years of diabetes, at least 50% of patients will have some sign of neuropathy. Because we don't frequently perform biopsies, it is impossible to know to what extent subclinical disease affects the nerve.



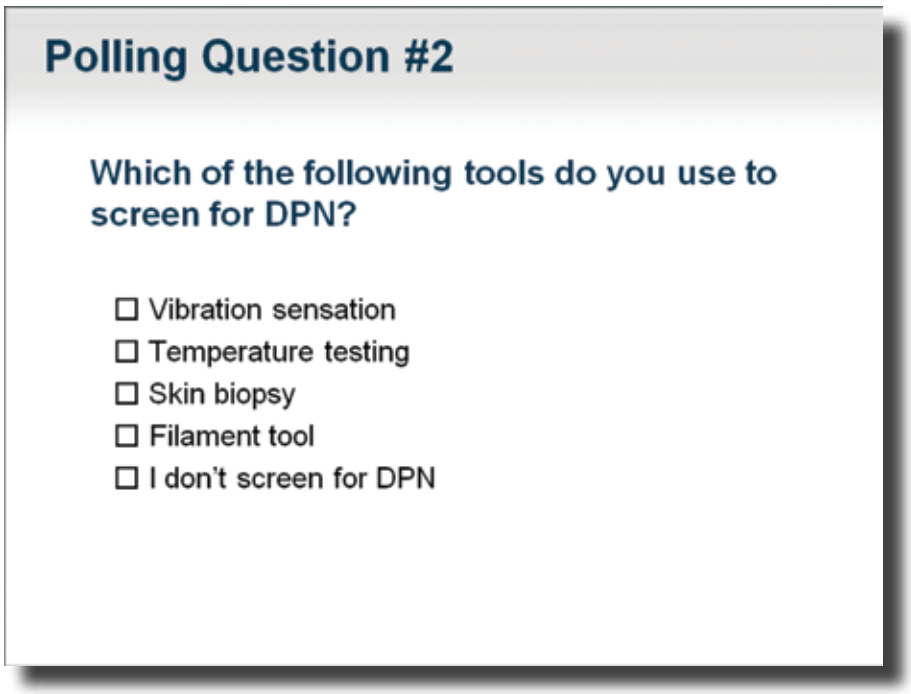
Slide 7.

We also know that there are people with impaired glucose tolerance who have abnormal nerve function and may actually have symptoms and signs [of DPN], which raises questions about the diagnostic criteria for diabetes because these people don't yet have diabetes. It is extremely unusual to have these kinds of signs and symptoms in people with normal glucose tolerance so in those situations, you need to look for other causes of neuropathy.



Slide 8.

The term neuropathy is descriptive; it shows that you have demonstrable clinically evident abnormalities in nerve function, usually in the peripheral nerves. But you can have abnormal central nerves, some cranial nerves, and so on. The neuropathic disorder includes manifestations in somatic and also autonomic function, which can be actually very serious from the patient's perspective.



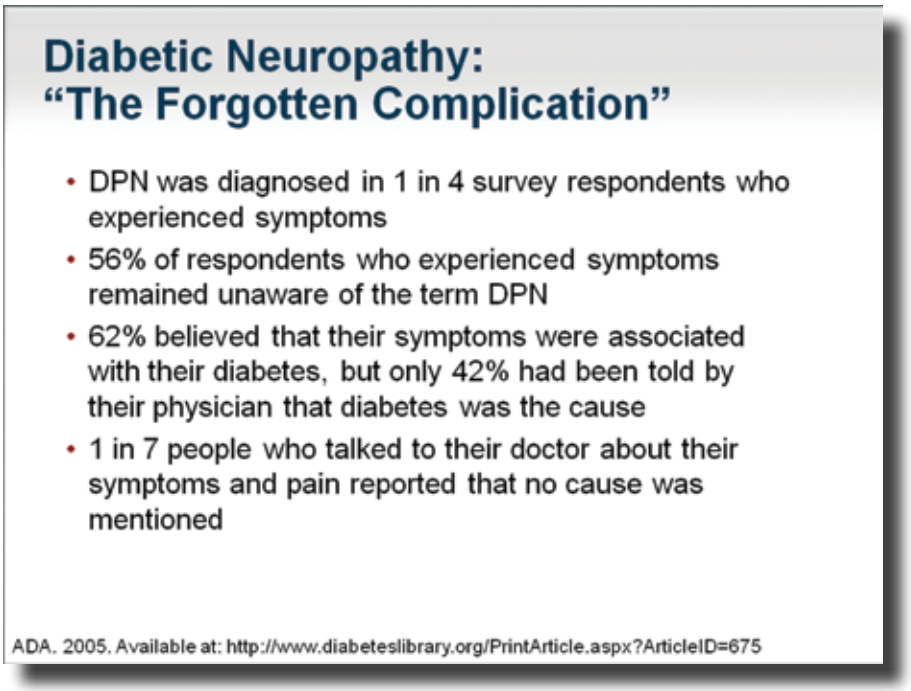
Slide 9.

Dr. Boulton: Let's pause for our next polling question.

Which of the following tools do you use to screen for DPN?

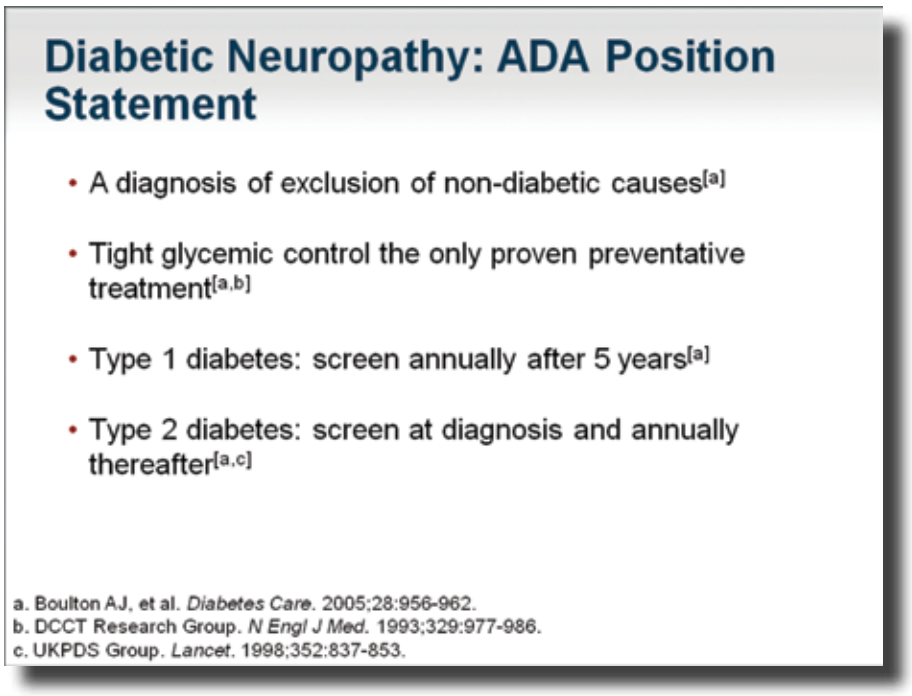
- Vibration sensation
- Temperature testing
- Skin biopsy
- Filament tool
- I don't screen for DPN

Diagnosis and Screening



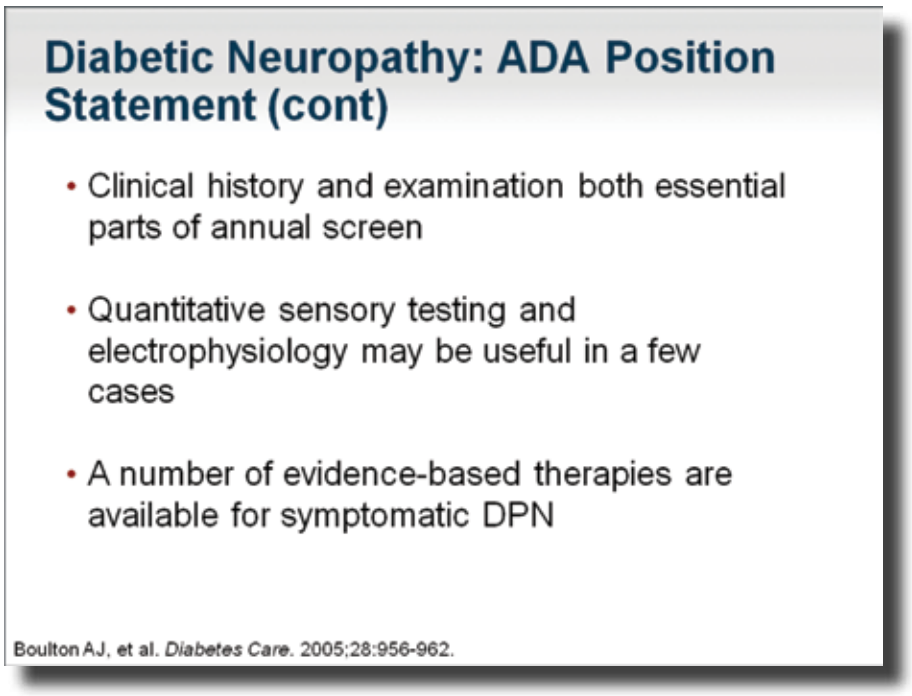
Slide 10.

I'd like to draw your attention to a survey done by the American Diabetes Association (ADA) 6 years ago because it provided some rather worrisome results. This was a telephone survey of [8119] patients with diabetes. Only 1 in 4 of the survey respondents who had experienced the symptoms of DPN had actually been diagnosed with the condition; this is extremely worrisome. The majority of respondents who experienced symptoms remained unaware of what the term DPN was and what it meant. Nearly two thirds of respondents (62%) believed that their symptoms were associated with diabetes, but less than half (42%) had been told by their doctor that diabetes was actually the cause. Finally, approximately 1 in 7 people who said that they had talked to their doctor about their symptoms and pain reported that no cause was actually mentioned. [These data tell us that] we have a lot of work to do in terms of education, not only of our patients, but also of our colleagues.



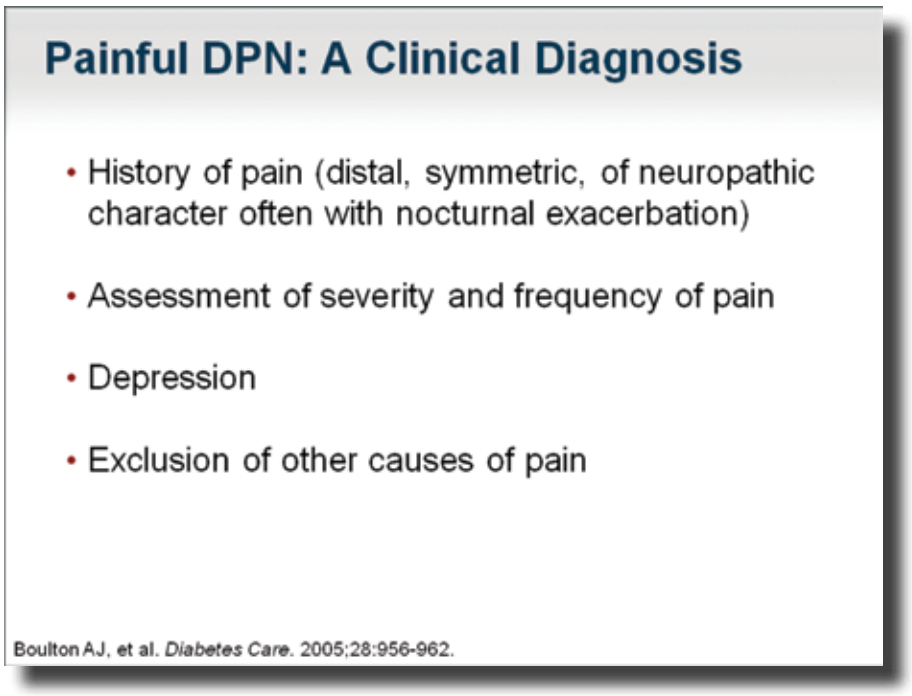
Slide 11.

A few years ago [2005], I was the co-chair of an ADA statement committee on diabetic neuropathies that was published in *Diabetes Care*. To summarize this statement, we concluded that DPN is a diagnosis of exclusion of non-diabetic causes. Some people will say to me, "Let's send them for electrophysiology or quantitative sensory testing to diagnose their condition," but that doesn't diagnose neuropathy; it just tells you there is a disorder of the nerve. Therefore, DPN is a diagnosis of exclusion and that is very important to remember. We also confirmed that tight glycemic control is the only known preventative strategy. We know from studies like the DCCT [Diabetes Control and Complications Trial] that good control can reduce the incidence of diabetic neuropathy by up to 60%. Patients with type 1 diabetes should be screened for evidence of neuropathy by careful examination of the lower limb annually after 5 years of diabetes. However, in type 2 diabetes, our study, the UKPDS [United Kingdom Prospective Diabetes Study], showed that nearly 13% of patients with a diagnosis of diabetes had significant neuropathy, even putting them at risk for foot problems so patients with type 2 diabetes should be screened for evidence of neuropathy at diagnosis and annually thereafter.



Slide 12.

We also confirmed that DPN in clinical practice is a clinical diagnosis so history and examination are both essential parts [of the annual screen]. However, you cannot diagnose neuropathy by history alone because many patients may have significant sensory loss but no symptoms whatsoever. Quantitative sensory testing and electrophysiology might be useful in only a few cases and there are a number of evidence-based therapies available for the treatment of symptoms of neuropathy.

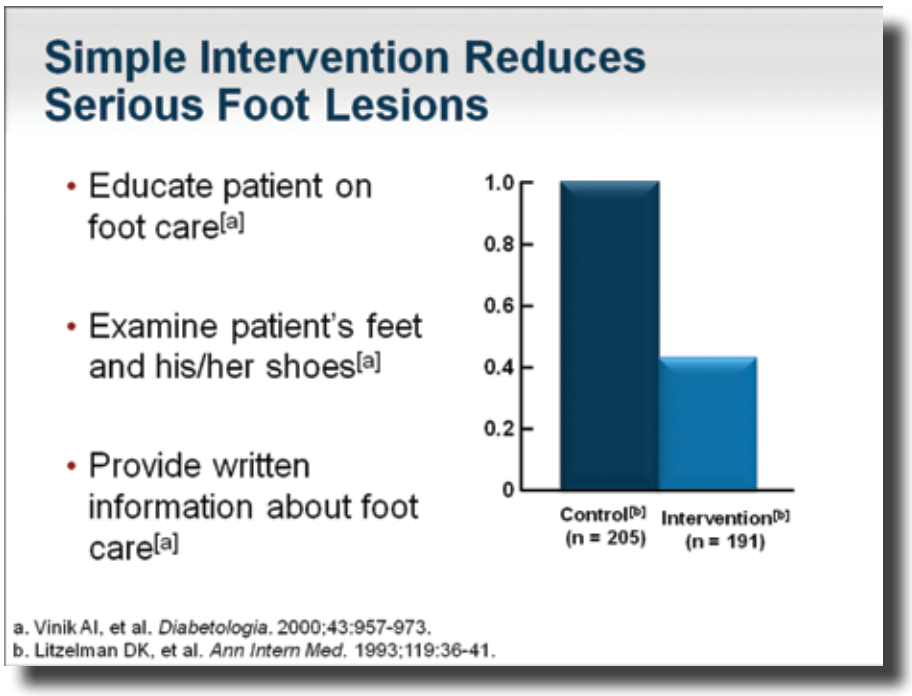


Slide 13.

To summarize, in clinical practice, DPN is a clinical diagnosis. To assess pain, we are looking for distal, symmetric, and neuropathic character. Usually these symptoms are worse at night. They are recognized to be associated with diabetes but symptoms may occasionally be present even in the absence of signs of early neuropathy. We should assess the severity and frequency of pain in those patients who have symptoms. For example, a simple 10-cm graphic rating scale can be used. We need to remember that this might affect affect, so patients may have depression or symptoms of anxiety, which should be inquired about. Finally, we need to exclude other causes of pain and again to recognize that DPN is a clinical diagnosis. What tools do you use in your clinical practice in screening for neuropathy?

Slide 14.

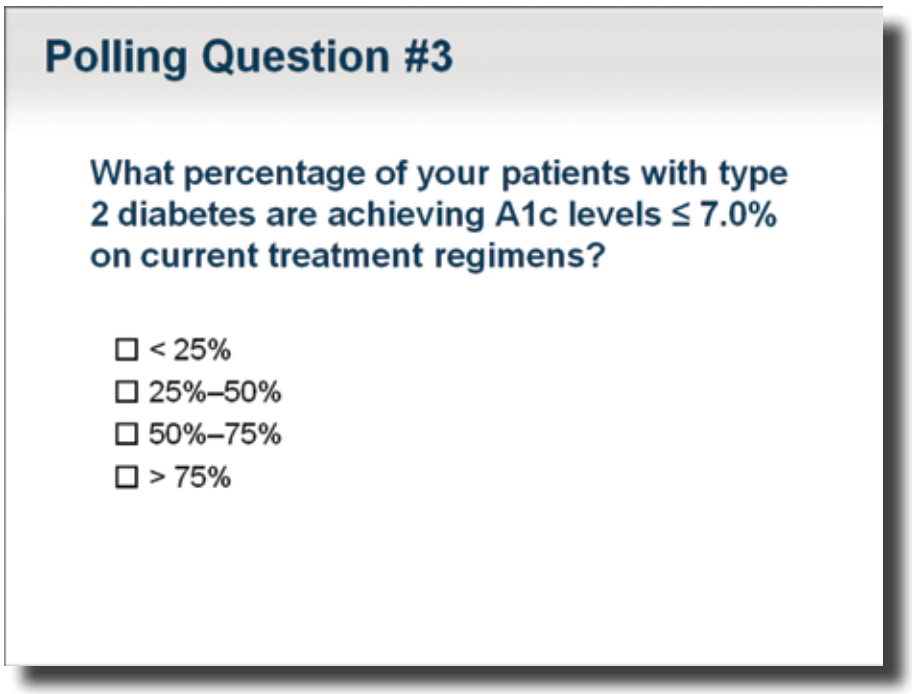
Dr. Fonseca: History as you said, is important but doesn't always tell you everything. What has become fairly standardized these days and quite popular, partly related to campaigns from organizations like the ADA and others, is the use of the monofilament. What this tool has allowed us to do is to give an estimation of sensation to fine touch in a very standardized way, with a certain degree of feeling that can be reproducible from patient to patient. It also tells us that if you can't feel the sensation, you are at higher risk for amputation. There is a misconception that if your monofilament test is okay you don't have neuropathy, but this is not the earliest abnormality seen in neuropathy. In fact, vibration sense can be lost before you lose sensation. But this is very easy to use; you don't need a fancy tuning fork. In addition, these monofilaments are now available in most doctors' offices.



Slide 15.

Once you establish a lack of sensation in the patient's foot, you can educate him or her about foot care. Patients become eligible in systems such as Medicare, for example -- Medicare pays for footwear that may be more appropriate. We teach patients to examine their feet and their shoes because they may not feel where they are ill-fitting. We also give patients information about their feet. So, the monofilament is a simple test that is very widely used.

Dr. Boulton: I would like to add and to remind our viewers that the monofilament, as Vivian said, does not actually exclude neuropathy if the patient can feel it. This is really a test that we should all be using in the annual review to identify patients at risk for foot problems.



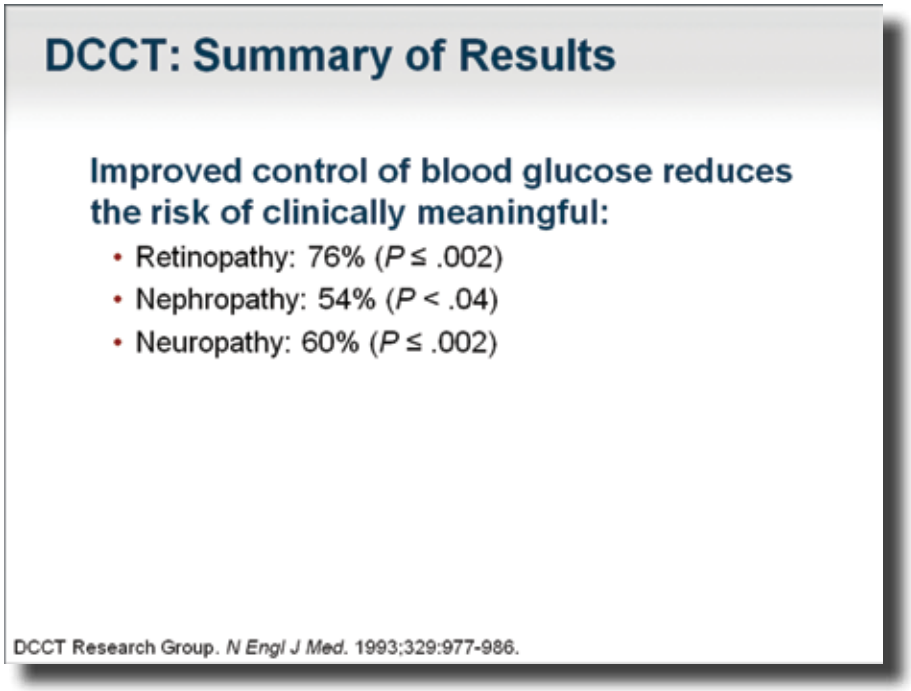
Slide 16.

Before I ask Vivian to continue our discussion we are curious to know what percentage of your patients with type 2 diabetes are achieving A1c levels ≤ 7.0% on current treatment regimens? Please click on your answer.

What percentage of your patients with type 2 diabetes are achieving A1c levels ≤ 7.0% on current treatment regimens?

- < 25%
- 25%-50%
- 50%-75%
- > 75%

Management of DPN



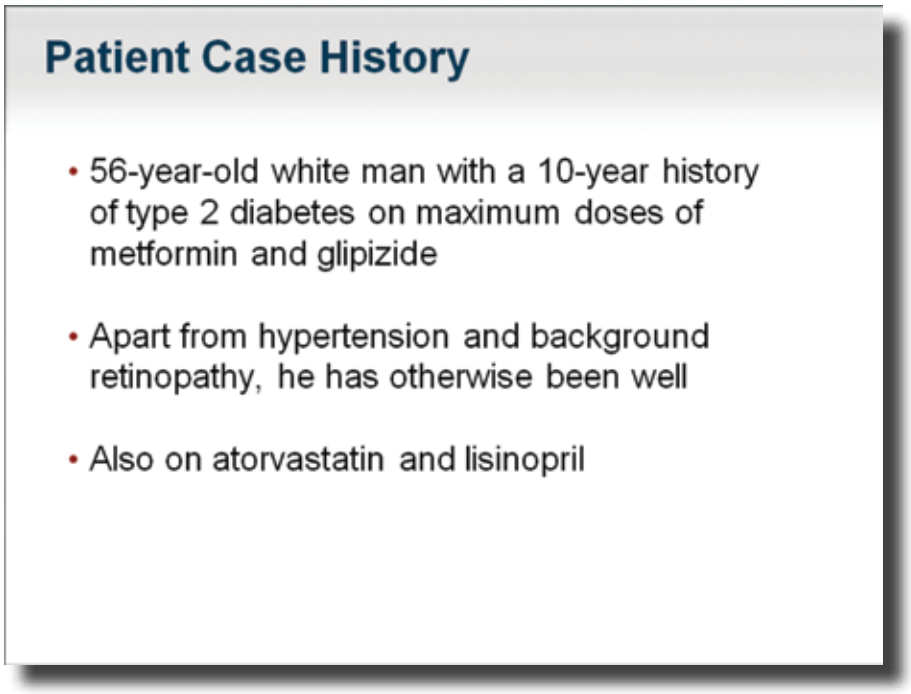
Slide 17.

I am going to ask Vivian to briefly summarize what I mentioned and alluded to earlier and that is the important DCCT study in type 1 diabetes and how intervention can help reduce complications.

Dr. Fonseca: The DCCT was the first study to clearly show that good control of diabetes prevented or slowed the progression of complications in people who already had them. Since we are talking specifically about neuropathy, there was a 60% reduction in diabetic neuropathy in patients whose A1c was reduced from 9% to 7% ($P \leq .002$). That is quite a remarkable finding; even in patients who had established neuropathy, [glycemic control] halted the progression so I think this is something well worth doing in most of our patients. A few people actually felt better as their diabetic control improved. Occasionally people will get transiently worse, but in general people do better.

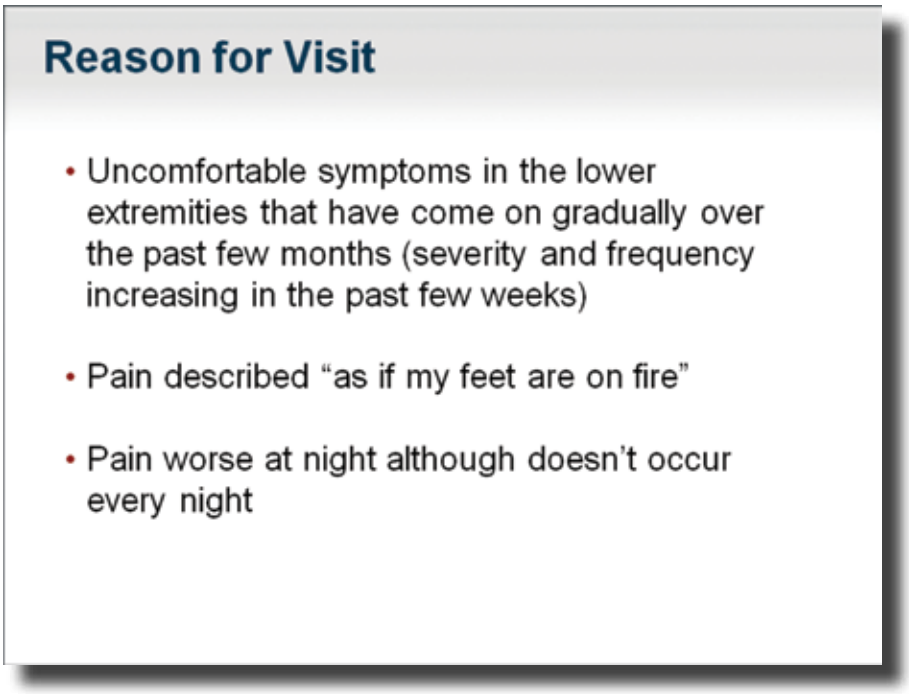
Dr. Boulton: I think it is important to emphasize that glycemic control is probably also highly relevant in type 2 diabetes. We don't have such good evidence as the DCCT but there are some studies that show that [glycemic control is beneficial in type 2 diabetes as well].

Patient Case Presentation



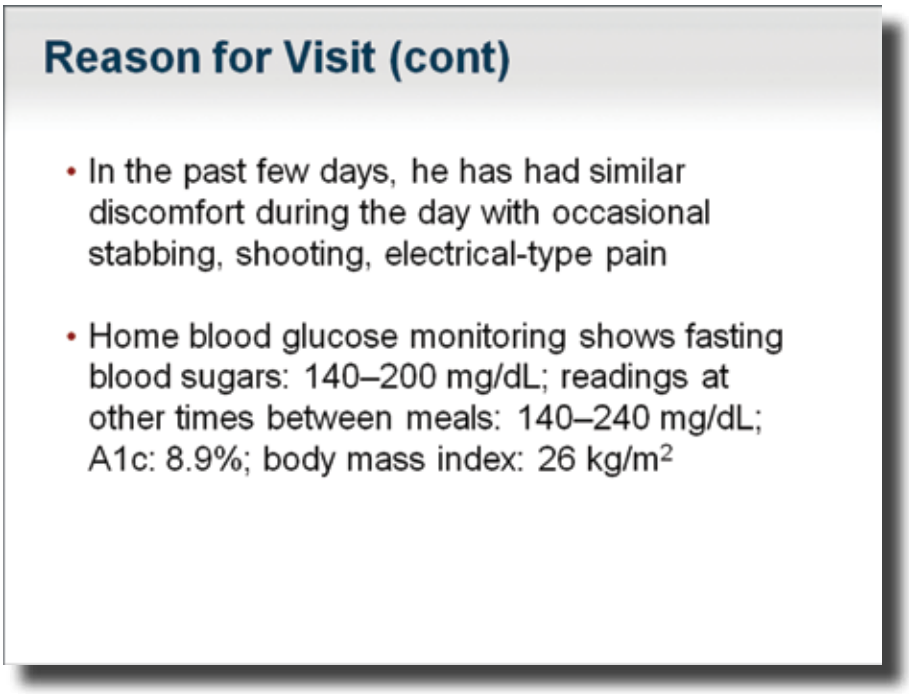
Slide 18.

To help to put all of these data into clinical perspective, we would like to present a patient case to see how you would treat this patient. Here is the history and it is not an atypical history of someone presenting to primary or secondary care. Our patient is a 56-year-old white man with a 10-year history of type 2 diabetes on maximum doses of metformin and glipizide. Apart from hypertension and background retinopathy, he has otherwise been well. He is also taking, as most of our patients are, atorvastatin and lisinopril.



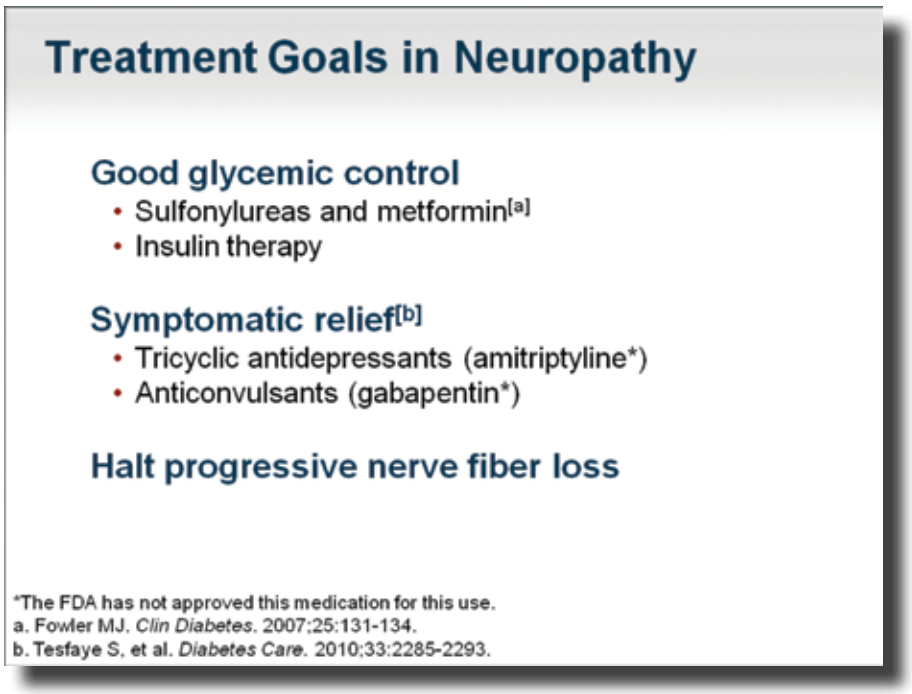
Slide 19.

The reason for his visit is that uncomfortable symptoms in the lower limbs developed that had come on gradually over the past few months with the frequency of these symptoms increasing, especially over the past few weeks. When asked to describe the pain he describes it as both feet up to the ankle level as being on fire. He says "my feet feel during the night as if they are on fire." The symptoms are much worse at night, although they don't necessarily occur every night.



Slide 20.

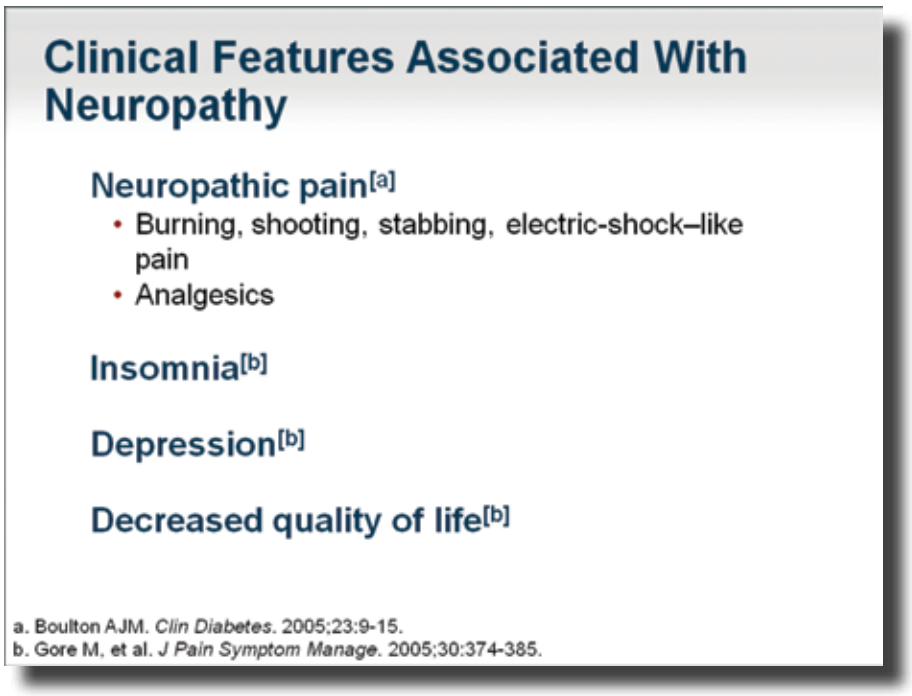
In the past few days, he has had similar discomfort during the day with occasional stabbing, shooting, and electrical type pain. His home blood glucose monitoring shows fasting blood sugars of 140-200 mg/dL and readings at other times between meals up to 240 mg/dL. His A1c is 8.9%, but his body mass index is rather low for someone with type 2 diabetes at 26 kg/m^2. So based on this patient's presentation, how would you approach this case?



Slide 21.

Dr. Fonseca: I am faced with 2 issues with this particular patient. First, his glycemic control is very poor; his A1c is 8.9%. It is interesting that he is not obese so maybe he is not that insulin resistant. Today, we have newer agents to treat diabetes in addition to sulfonylureas and metformin, which tend to lower A1c by about 1 percentage point. This patient needs about a 2 percentage-point reduction so I would really consider insulin therapy in this particular patient. But, we can't wait for the improved glycemic control to alleviate his symptoms; it is going to take a long, long time but we have a range of treatments as you said. We don't have specific treatments that change the natural history of peripheral neuropathy, other than provide good control. While we are not correcting the neuropathy we can give this patient symptomatic relief. Traditionally we used tricyclic antidepressant drugs such as amitriptyline*, etc, at night but they have a lot of side effects. We then moved on to using anticonvulsants like Neurontin® [gabapentin*], but now there are US Food and Drug Administration (FDA)-approved medications for pain. They take away the pain without actually changing the neuropathy. My goal in this patient is to improve his glycemic control to halt progressive nerve fiber loss so that we can avoid amputation and further progression of the disease.

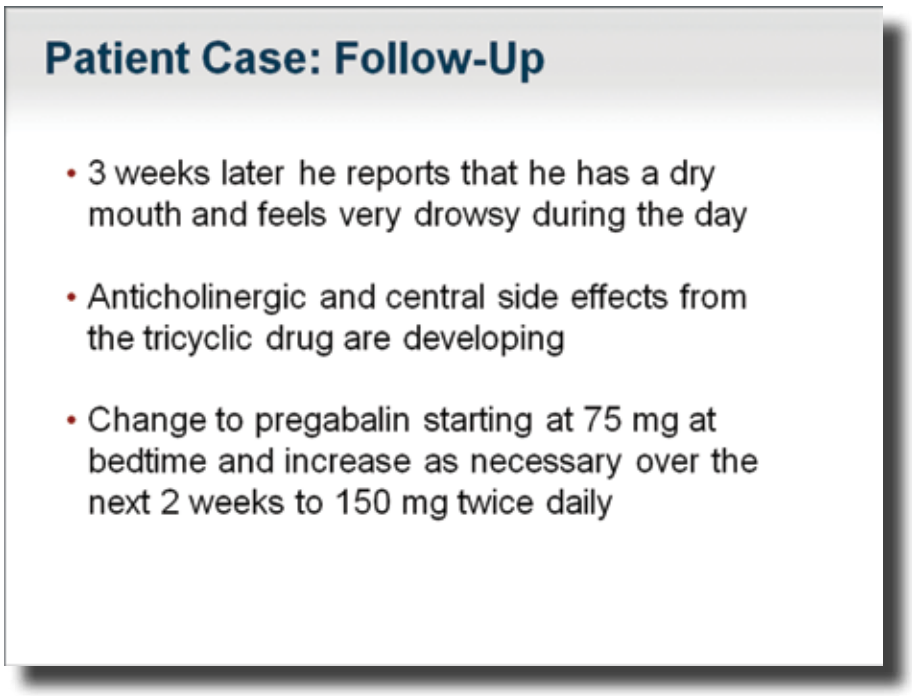
[Editor's Note: tricyclic antidepressants such as amitriptyline have anticholinergic effects that may cause problems for patients with thyroid disease, orthostatic hypotension, or impaired liver function. These agents are contraindicated in patients with heart disease.[6] The efficacy of amitriptyline vs pregabalin was compared in a 5-week randomized, double-blind, crossover, active-control, clinical trial with variable dose titration in 51 patients.[7] There was no significant difference between pregabalin and amitriptyline in the main outcome of pain relief. Good pain relief was reported in 48% and 34% of users of pregabalin and amitriptyline, respectively, but was associated with a higher rate of adverse events. Of the 52 adverse events reported, 34 (65.4%) were with amitriptyline. The most frequent adverse events associated with tricyclic antidepressants include drowsiness and dry mouth.]



Slide 22.

He has classic symptoms of neuropathic pain. He has a burning, shooting, stabbing pain, particularly at night, and these electric-shock-like pains are very characteristic of patients with neuropathy. It is due to injury of the peripheral nerves, which happens in conditions like trigeminal neuralgia and is very acute and localized. In DPN, it is more generalized and peripheral so we can sometimes use analgesic therapies. I tend to avoid opiates because patients get somewhat addicted sometimes, but in very severe cases, we may want to consider that. I would also like to assess this patient for other things such as insomnia. Is he not sleeping well? This would have an effect on depression and quality of life, both of which are very important.

Dr. Boulton: Right. I think it is important to remind the viewers that neuropathic pain is difficult to describe. Patients are used to having injuries, falls, trips, banging their head and they can describe that pain. But because this is atypical and very difficult and a new experience this is why we have such a broad spectrum of symptoms that our patients describe. So it can be difficult to get a history for the patient to actually describe the pain because it is a new experience.

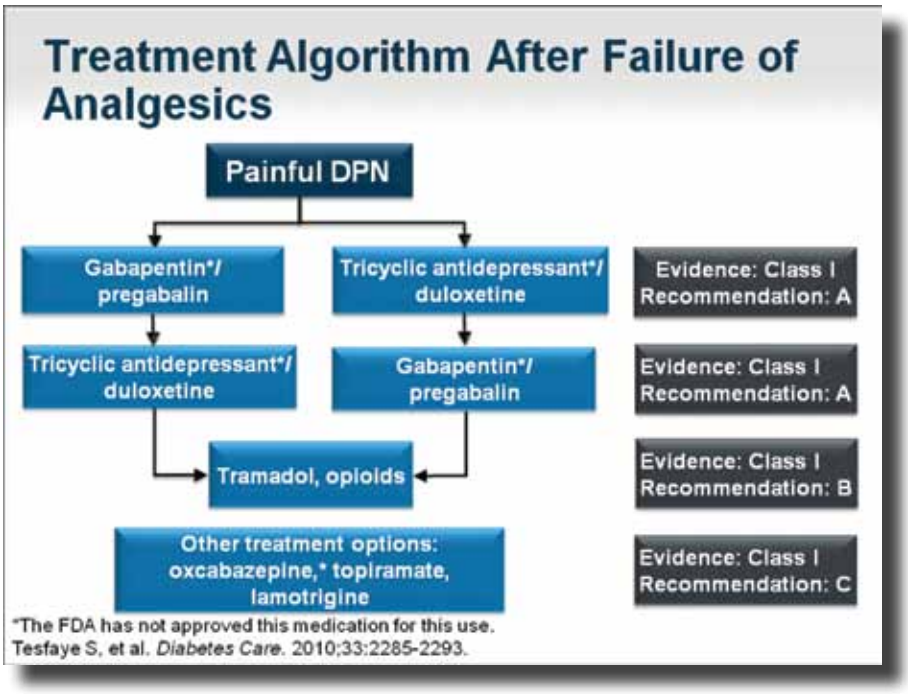


Slide 23.

Let's return to this gentleman. Three weeks later, he reports that he has a dry mouth and has been taking amitriptyline or 1 of the tricyclic antidepressants. He feels very drowsy during the day. What would you think should be the next step in this particular case?

Dr. Fonseca: This is a common side effect of drugs like amitriptyline. Because of these anticholinergic and central effects of the drug, I tend not to push the doses too high for that reason. Some anticonvulsants can also help. Pregabalin, which actually started off under clinical development as an anticonvulsant but is now approved for pain and a number of other conditions, can help. I start with a low dose and after 2 weeks, increase the dose.

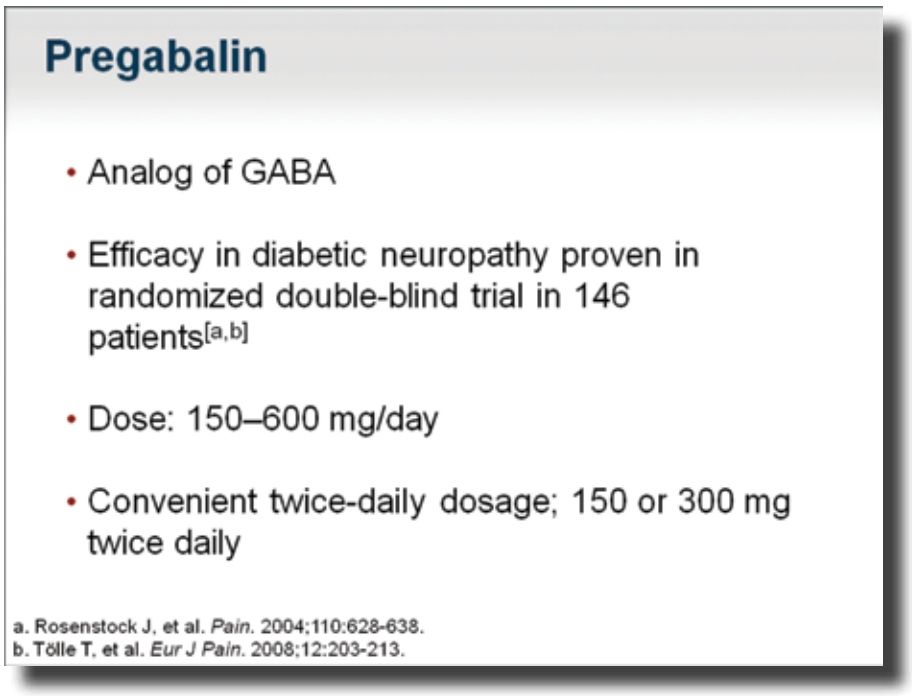
Treatment Options



Slide 24.

Dr. Boulton: Dr. Fonseca mentioned pregabalin and this, as he said, is one of the drugs licensed in this country specifically for neuropathic pain. One of the other ones for neuropathic pain is the dual inhibitor duloxetine, which also has proven efficacy with level A evidence, which means [its efficacy has been proven in] multiple randomized control trials. A treatment algorithm that was published just recently [October 2010] by an international group in which I chaired the session on painful neuropathy is shown on this particular slide. We have a choice of pathways we can take with someone presenting with painful peripheral neuropathy. One track would have the patient starting off on a tricyclic antidepressant, duloxetine, whereas in the other pathway, the first choice could be an anticonvulsant such as gabapentin* or pregabalin. All of these drugs have level A evidence, or multiple randomized control trials [to support their use]. If the patient fails on one of these 2 agents, we can try the other. So if the patient who is started on an anticonvulsant doesn't show benefit, we can try one of the antidepressants. Other drugs that have proven efficacy for patients who do not respond to either of these 2 groups would be the synthetic opiates such as tramadol, which is a level B recommendation. But as you rightly said, these agents have the worrisome potential for being addictive. There are other treatment options [oxcarbazepine*, topiramate, lamotrigine], and the reference is on this slide.

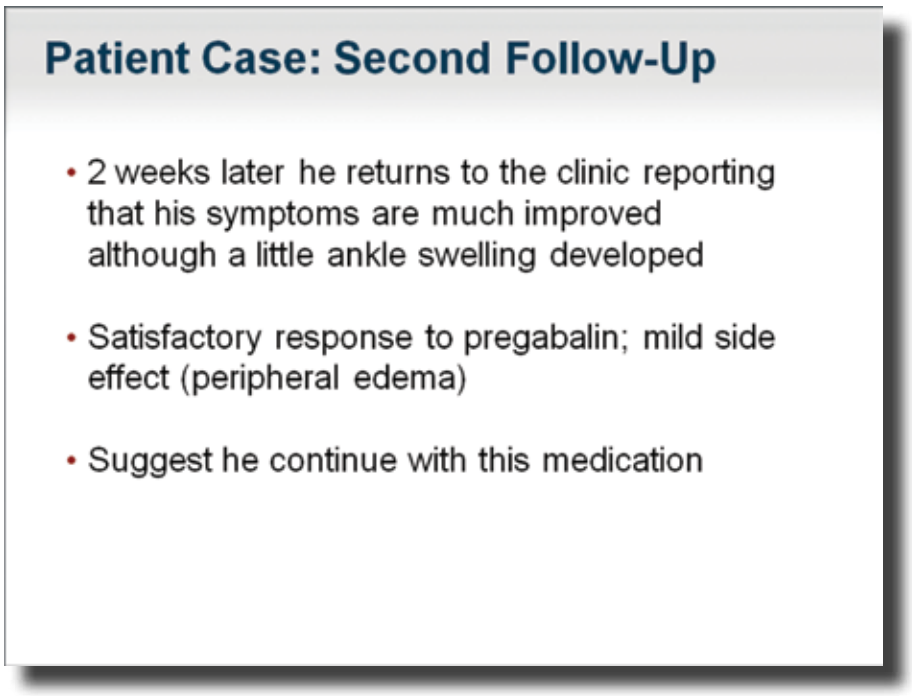
[Editor's Note: Gabapentin is an anticonvulsant approved by the FDA as an adjunctive medication to control partial seizures and may be prescribed off-label for painful neuropathy. In a randomized, double-blind, placebo-controlled, 8-week trial, gabapentin, compared with placebo, showed a small effect of net pain reduction from baseline of 11% on the 11-point Likert scale and improvement in quality of life, in subsets of mental health (P = .03) and vitality (P = .001).[1] Dizziness occurred in 20 (24%) patients in the gabapentin group vs 4 (4.9%) in the control group; P < .001) and somnolence occurred in 19 (23%) patients in the gabapentin group vs 5 (6%) in the control group; P = .003). In a separate study, gabapentin showed no effect.[2] Duloxetine is a serotonin-norepinephrine reuptake inhibitor and the first drug approved by the FDA for painful diabetic neuropathy. The efficacy and safety of this agent has been evaluated in a 12-week, double-blind, randomized, placebo-controlled trial in 348 patients with pain due to peripheral neuropathy caused by type 1 or type 2 diabetes.[3] The primary outcome measure was mean score of 24-hour average pain severity evaluated on an 11-point Likert scale. Duloxetine reduced pain by 8% on the 11-point Likert scale; quality of life was not measured. In a separate study, pain severity, rather than variables related to diabetes or neuropathy, appeared to predict the effects of duloxetine in diabetic peripheral neuropathic pain.[4] Patients with higher pain severity tended to respond better than those with lower pain levels. The most frequent adverse events associated with duloxetine include nausea, somnolence, dizziness, diarrhea, constipation, dry mouth, and reduced appetite. These adverse events are usually mild to moderate and transient.]*



Slide 25.

Pregabalin is an analog of GABA [gamma-aminobutyric acid], an antiepileptic for complex-partial seizures and an analgesic. Its efficacy has been shown in multiple trials and pooled analysis. The doses are 150 to 600 mg daily, which can be given twice daily, but as you correctly said, we all have learned to start it low, at 75 mg. Most patients will require a dose of 150 or 300 mg twice a day.

[Editor's Note: The efficacy and safety of pregabalin was reported in a pooled analysis of 7 studies over 5–13 weeks in 1510 patients with DPN. Response rates defined as ≥ 50% pain reduction from baseline to endpoint were 47% (pregabalin 600 mg/day), 39% (pregabalin 300 mg/day), 27% (pregabalin 150 mg/day), and 22% (placebo).[5] The most frequent adverse events for pregabalin 150-600 mg/day included dizziness, somnolence, peripheral edema, headache, and weight gain.

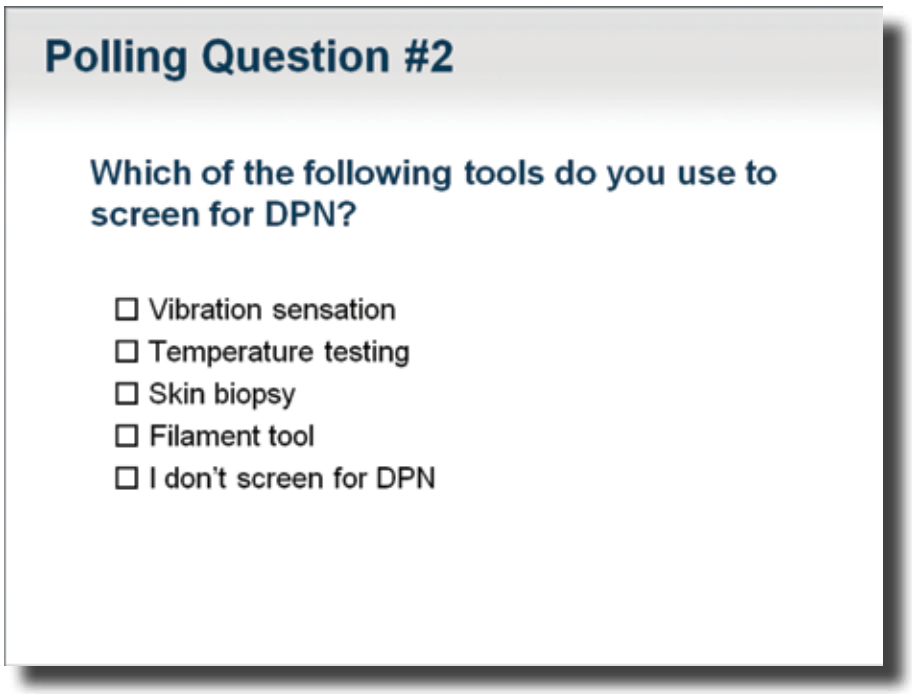


Slide 26.

Two weeks later, our patient returns to the clinic reporting that his symptoms are improved, although a little ankle swelling developed. What do you think should be our next step in this gentleman?

Dr. Fonseca: I am pleased that he has had a satisfactory response to pregabalin, but he has a side effect that is quite common, which is fluid retention. Another common side effect is weight gain. I tend to watch for these symptoms because I am very conscious of patients who are overweight. This is not the case for our patient because his body mass index is low, but I do watch for possible weight gain and may consider using duloxetine because it does not cause weight gain, or not to the same degree anyway. That is certainly a consideration. One thing I want to emphasize is that we are only treating the pain; we are not treating the neuropathy. Sometimes patients have numbness but we don't really have a good treatment for that so I think it is very important to realize that we need treatment strategies that change the natural history.

Dr. Boulton: Absolutely and there have been many, as we both know, pathogenetic treatments that have been tried in trials over the at least 20 or 30 years and certainly none has come really to market.

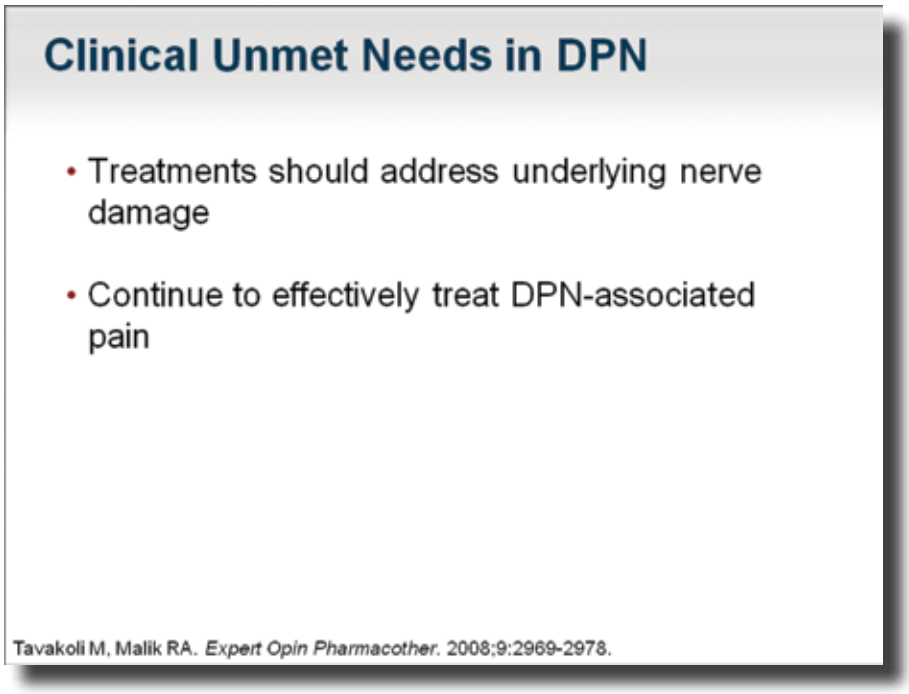


Slide 27.

Which of the following do you feel is the greatest barrier to treatment of DPN?

- Side effects of treatment
- Cost of treatment
- Lack of effectiveness of current treatment
- Pill burden
- I don't treat DPN

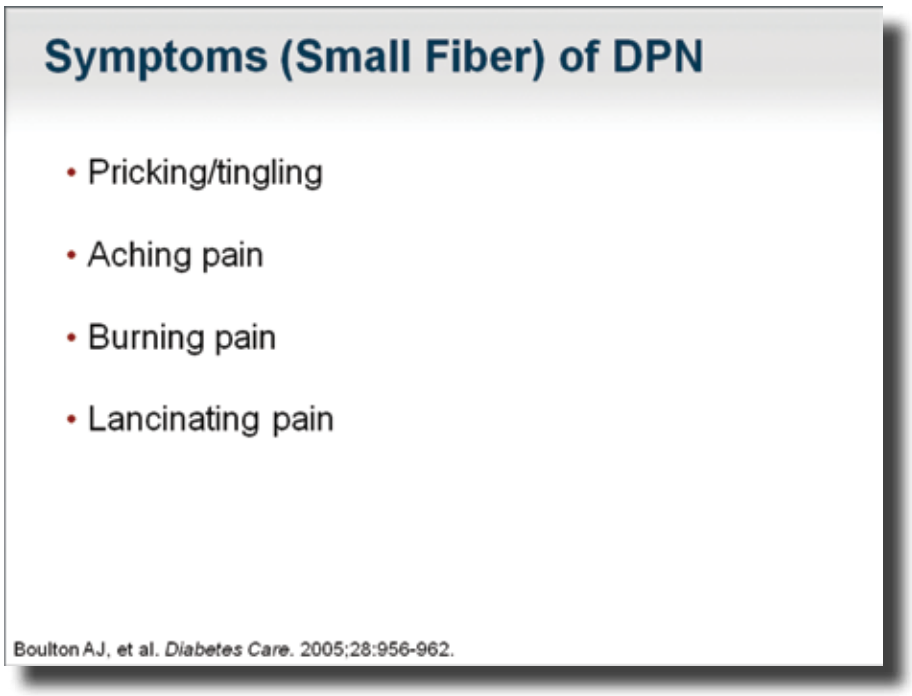
Newer Therapeutic Approaches



Slide 28.

Vivian, what do you feel are some of the challenges with current treatment options?

Dr. Fonseca: As I said, we are not treating the natural history [of DPN] and we are not changing the neuropathy so I would like to see newer treatment options. We have a wide range of treatments for pain, which I think is great because 10 or 15 years ago, a large number of patients would come to our clinic mainly because they were in pain. Now these patients are getting treated in primary care and they are not suffering as much in regards to pain. There is no one single treatment to recommend as we've discussed but there are different options, which is good, but we need to look at other aspects of therapy.

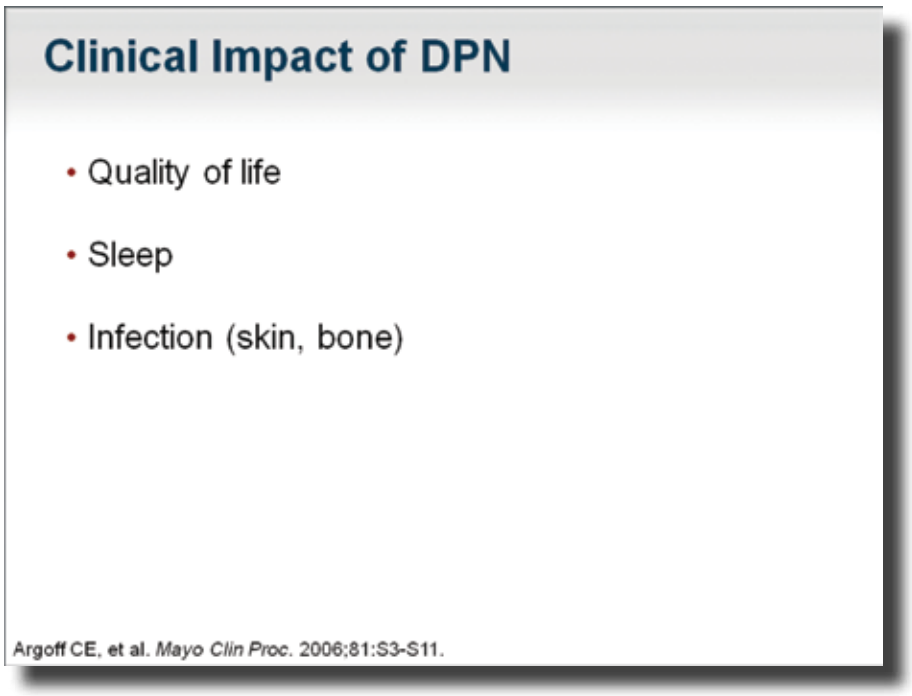


Slide 29.

We also need to emphasize that there are different kinds of pain and different kinds of symptoms. One treatment may not suit all and sometimes dissecting this can be difficult.

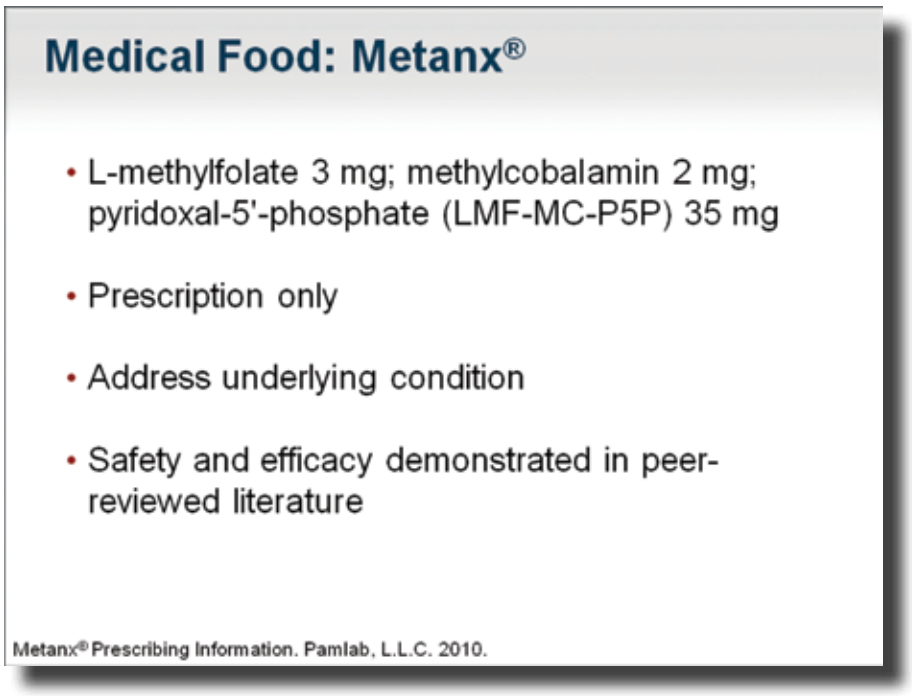
Dr. Boulton: I think one of the problems we have is that we don't know which drug necessarily works for which symptoms.

Dr. Fonseca: That is absolutely a trial and error. Which drug works best for which type of pain (the pricking, tingling, aching, or lancinating pain), we don't really know. Then we have this problem of numbness. What do we do about numbness? Right now, the best thing to do about it is to teach the patient to take care of that to prevent ulceration. This means getting the appropriate footwear made and using inserts and padding. It is very, very important in preventing amputation, which is essentially the goal. All of this is actually covered by many insurance plans and Medicare once you establish the diagnosis of neuropathy, so it's very important to first make the diagnosis.



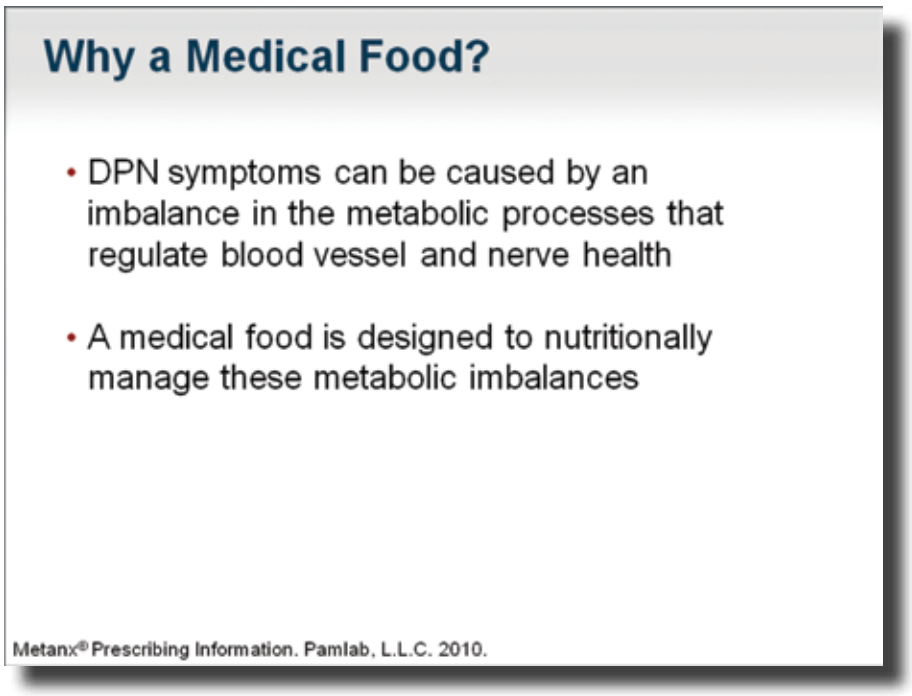
Slide 30.

So we talked about the pain aspect and the numbness, but there is also the thing about the pain affecting the quality of life and the patient's sleep patterns being disturbed. [Then there is] the fact that they may get infections when they have ulceration and trying to get that treated, avoiding osteomyelitis. Once it progresses, it is very hard to treat.



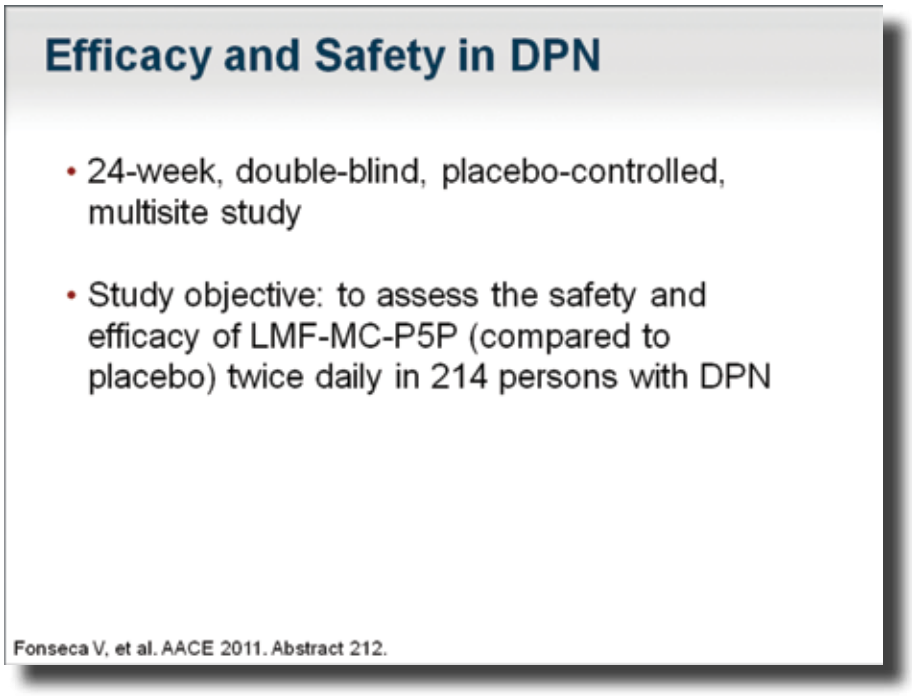
Slide 31.

I want to present some data that we just presented at the American Diabetes Association Meeting [and American Association of Clinical Endocrinologists (AACE) meeting] in San Diego, 2011 on a natural product. It is called Metanx®, which is actually the generic name. It is a combination of L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate (LMF-MC-P5P). Essentially, what this includes is the natural form of folate, vitamin B-12, and natural vitamin B-6. This is classified as a medical food. There is a subtle difference between a medical food and a prescription medicine and this falls somewhere in between so let me explain. A medical food is available only by prescription. You can't go and get it over the counter. You can get over-the-counter vitamins, you can get natural foods from the food you eat, but a medical food requires a prescription and supervision by a healthcare provider. This is because the doses are higher and different from over-the-counter medications. [LMF-MC-P5P] was developed to address some of the underlying pathophysiology of nerve function, which may result in changes in biomarkers of vascular function and endothelial function. To get something classified as a medical food, you need to demonstrate [safety and efficacy] in peer-reviewed literature.



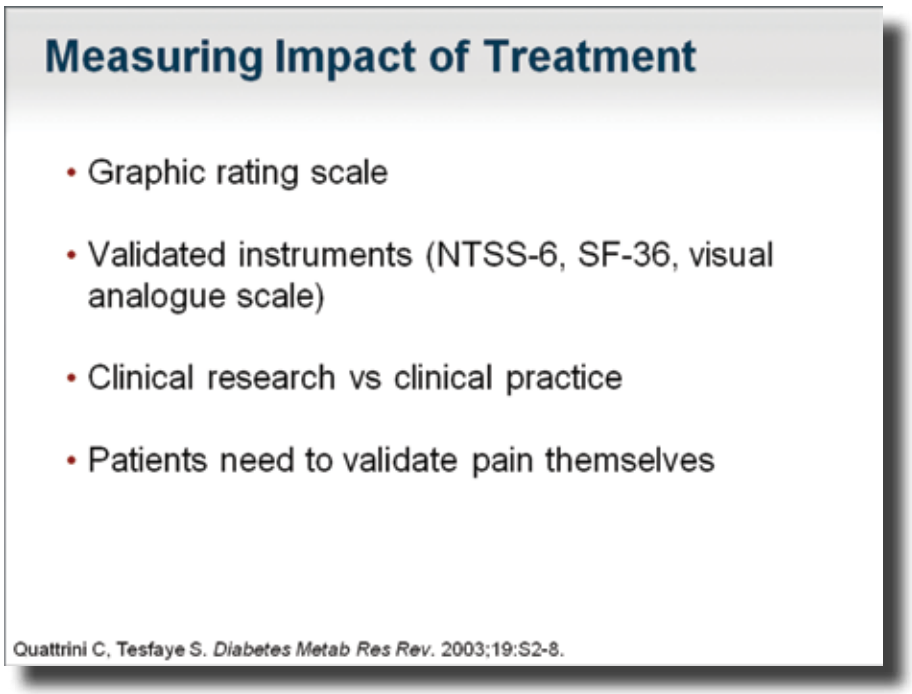
Slide 32.

Why was [LMF-MC-P5P] developed? I'm not exactly sure. It probably relates to the longstanding knowledge about how vitamin deficiencies lead to peripheral neuropathy and the possibility that there may be such metabolic imbalances in patients with diabetes. Or, it could be that by changing the vasculature and endothelial function with some of the ingredients in these vitamins, renal function is improved.



Slide 33.

What we did was a 24-week, double-blind, placebo-controlled, multisite study of [LMF-MC-P5P] in subjects with DPN. The objective was to see whether this particular medical food given twice daily would improve patient symptoms as well as improve vibration perception threshold. That is what we thought was the objective that we could use and we carried out this study in 214 patients with peripheral neuropathy.



Slide 34.

But measuring impact of treatment can be somewhat challenging. The nerve conduction doesn't change, none of the therapies have changed, so let me ask you as an expert in neuropathy about the various instruments that are used, such as quality-of-life assessments and symptoms scores. How useful can they be?

Dr. Boulton: There are a number of different ways to evaluate response to treatment in clinical practice and also in clinical trials. The most important thing to remember is that pain is a personal psychological experience and you cannot rely on an external observer to assess it. I look back at some of the trials and see that the physician's overall impression was improved but I have to say that this is completely irrelevant. Only the patient can tell you if the pain was better or worse. It is really important to measure pain and there are, as I mentioned before, a number of instruments such as the graphic rating scale, which is very simple to use. There are a number of validated instruments such as the NTSS-6 [Neuropathy Total Symptom Score-6]. There are also measures for quality of life, the generic SF-36 [Short Form-36] and there is a neuropathy-specific measure, NeuroQoL. There are a number of different measures that can be used, but the visual analog scale or the graphic rating scale remains the most important.

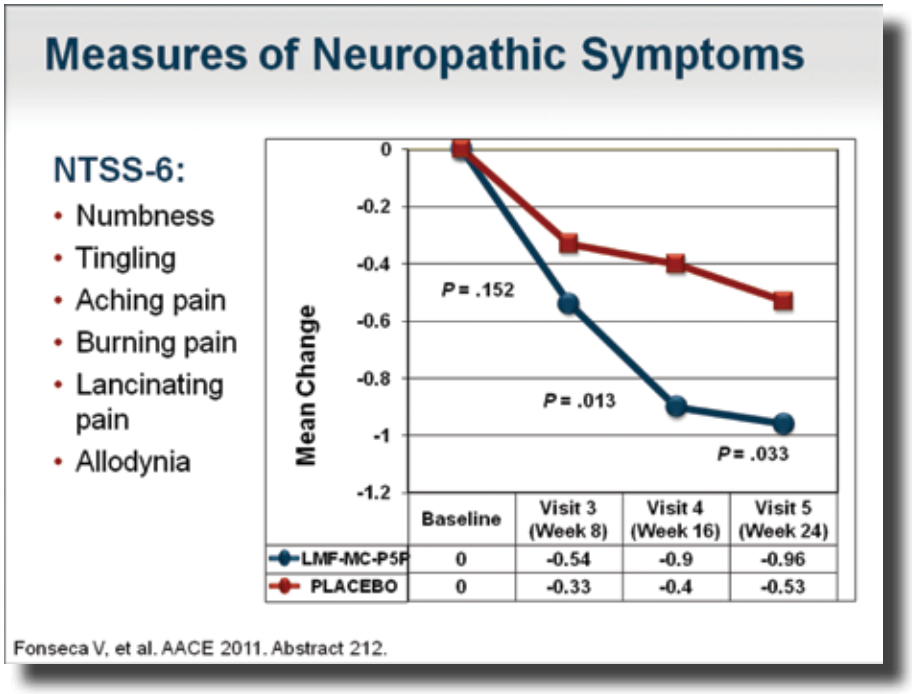
Dr. Fonseca: That is a practical instrument you can use in a clinic because some of these instruments are fine to use in research but may be too cumbersome to use in clinical practice.

Dr. Boulton: In clinical practice, all we need to do is give the patient a 10-cm line and ask them to mark along the line, the worst possible pain to no pain.

Dr. Fonseca: I have done this in research studies; it is quite remarkable how patients will shift over time. And only they can tell you, as you said.

Dr. Boulton: Exactly and we must remember that. If somebody comes to tell you and tells you this drug works because the doctor says it does, it can't be true. It might be true but we don't know so you can't believe that. You have to have the patient validate it.

Dr. Boulton: Tell us about your results.

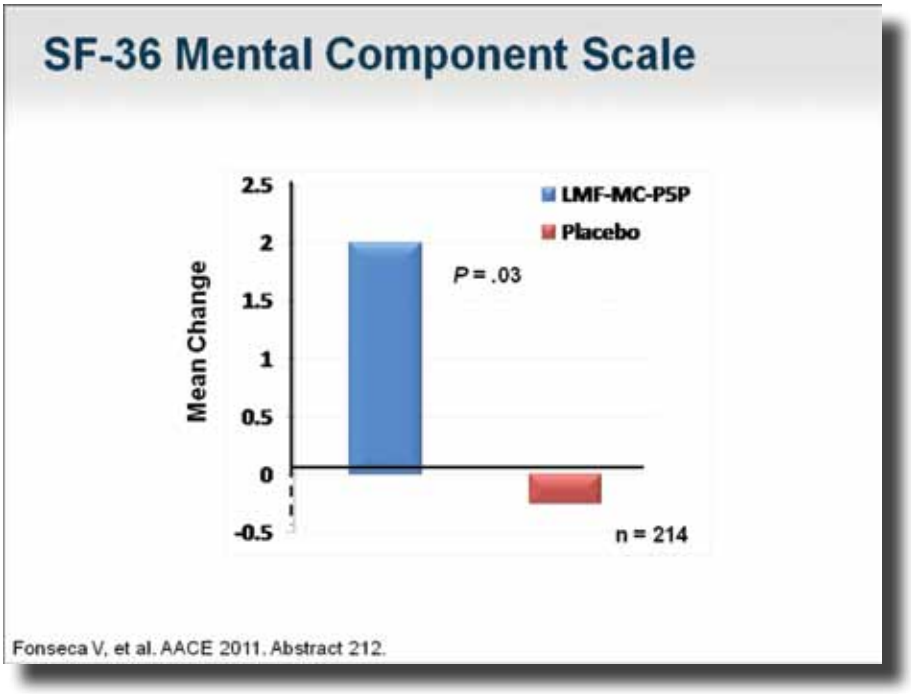


Slide 35.

Dr. Fonseca: The primary endpoint was a change in vibration perception using an instrument that measures it and this did not change significantly. It may be that it is impossible to change some of these physiologic tests for neuropathy. However, the NTSS-6, a test of 6 composite symptoms that gives you different scores in which the patient themselves write their scores, has been used in many clinical trials. What was shown was that after 16 weeks, there was a significant improvement with [LMF-MC-P5P] compared with placebo and this benefit was maintained to the end of the study at 24 weeks. This was statistically significant. Essentially, although the vibration didn't get better, the patients felt better.

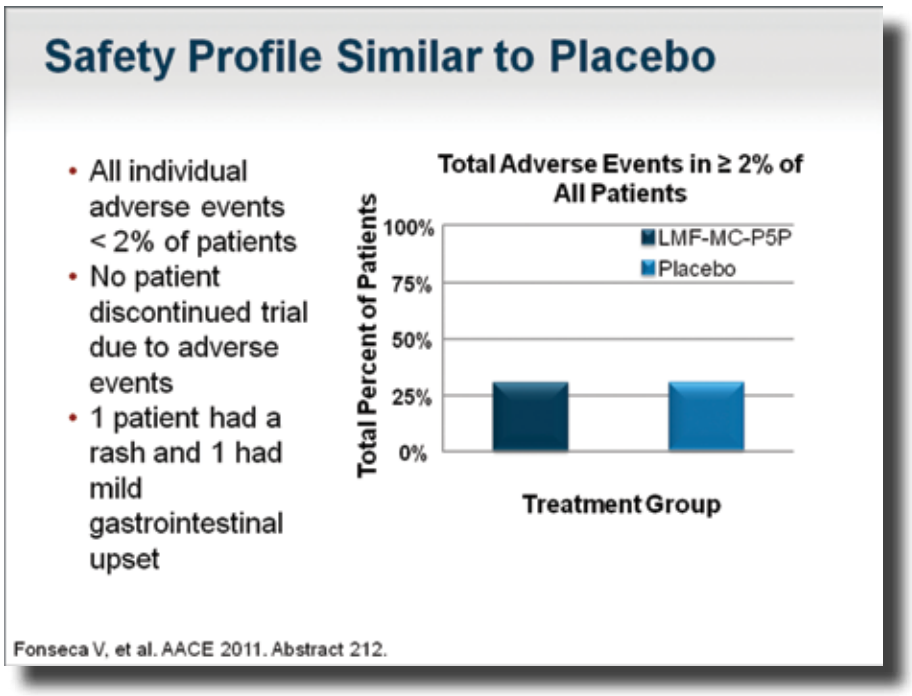
Dr. Boulton: So you did show a placebo response?

Dr. Fonseca: Yes, but it wasn't as great. So what are these 6 things? It consists of numbness, tingling, aching pain, burning pain, lancinating pain, and allodynia, which is when you feel things like the sheet on your feet when you are in your bed clothes. Essentially, the patients were feeling better in a number of different ways without us being able to pinpoint what way that was. As you pointed out, it is impossible for me to know how a patient is really feeling so we came up with a score based on what the patients told us that showed an improvement.



Slide 36.

We also looked at things like quality of life, the mental component of the SF-36, which showed a significant improvement while there was no change with placebo. That may well be that patients were now sleeping better at night so they naturally felt better and their overall functioning was better. The components of this test are general mental health, their emotional feelings, and social function, etc.



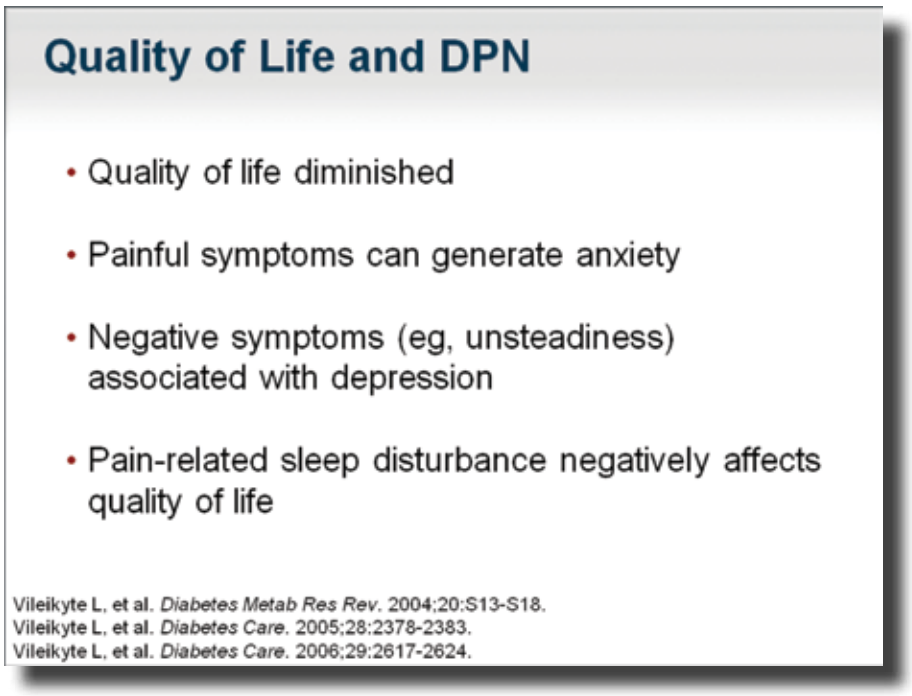
Slide 37.

It is important to talk about safety. There were no differences; they were exactly the same as placebo. Essentially very low —

Dr. Boulton: [interposing] That is very important because most of the drugs we use for neuropathic pain have side effects.

Dr. Fonseca: Yes and so it is nice to have this medical food. Of course it requires a prescription, but it doesn't appear to have any side effects. So no difference from placebo was seen. The overall adverse event rate reported was < 2% and none of those events were serious. Nobody discontinued their medication, which was actually very nice. One patient had a rash and one had mild gastrointestinal side effects.

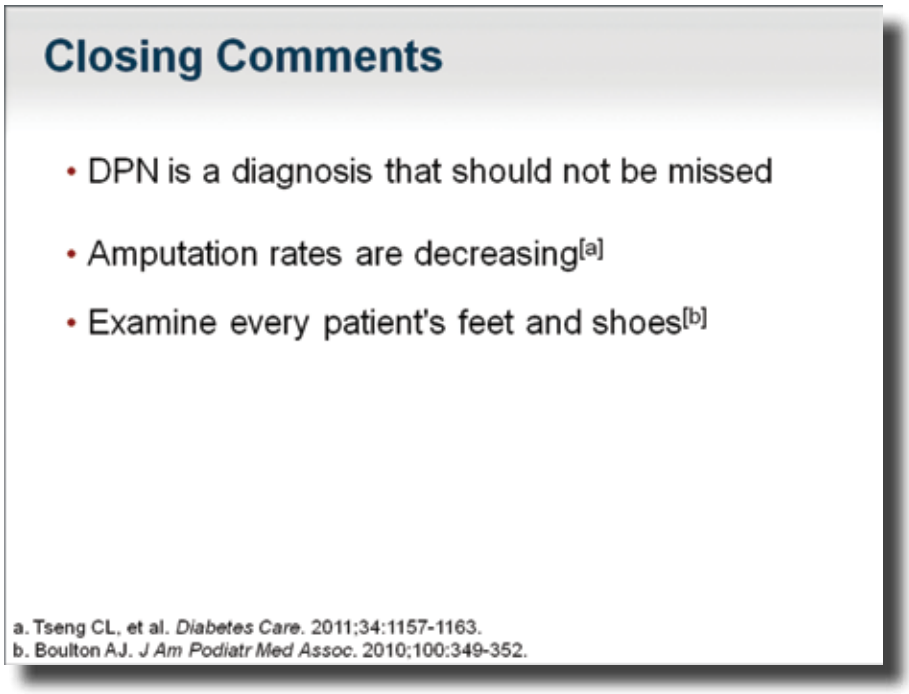
What do you think about quality of life, could you tell us how this affects neuropathy?



Slide 38.

Dr. Boulton: Quality of life is a major feature that needs to be taken into account in all studies such as this one and you did that. We know that quality of life is diminished in patients with painful neuropathy, which is hardly surprising. Painful symptoms can also generate anxiety and worry that there is something very seriously and significantly wrong with this chronic persistent pain. Another negative symptom such as numbness that has come out in some of our studies is unsteadiness, which has been highly prevalent. Patients with trips and falls are associated with depression. Therefore, both anxiety and depression will affect quality of life, which could be further compounded by terrible sleep disturbance from the burning pain at night. These are all very important.

Closing Comments



Slide 39.

To summarize what you've said, there is a symptomatic response with [LMF-MC-P5P] and this is, indeed, interesting. There was also another paper that was presented at this meeting [71st Scientific Sessions of the ADA, June 24-28, 2011] with positive data on experimental neuropathy with the same agent.[8] I am going to ask Vivian for his closing comment and thank him for his expert insight. Do you have any closing comments?

Dr. Fonseca: First of all, I just want to emphasize that people should be looking for neuropathy and not missing this diagnosis because simply educating patients about it, giving them the opportunity to examine their own feet, encourage them to wear appropriate footwear, and going to the podiatrist will save amputations. I also want to point out we now have some recent data, as you well know, that amputation rates, at least in Europe and America are decreasing. This is the first time we have seen that. It is very reassuring for people like us who have worked in the field of diabetes for so many years where this has been a huge problem. I am very pleased to see that the rates are declining significantly.

Dr. Boulton: Perhaps a closing comment from me would be to remind everybody of the words of Dr. Paul Brand who worked in leprosy. When he was asked what is the most important thing we can do to reduce amputations in diabetes he said every time you see a patient with diabetes remove their shoes and socks and examine the feet.

I would like to thank you, Vivian, for your expert insight.

Closing Comments

Slide 40.

Thank you for participating in this CME/CE activity. To proceed to the online CME/CE test please click on the earn CME credit link on this page.

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Strategies for Early Detection, Prevention, and Treatment of DPN CME/CE

Eve J. Wilson, PhD
Posted: 08/16/2011

Background

Diabetes is an increasingly common disorder in the United States, with an estimated 25.8 million people, or 8.3% of the population, now affected.[1] In 2008, the incidence of new cases was 8 in 1000; recent studies project that this figure will nearly double by 2050, by which time as many as 1 in 3 individuals in the United States may have diabetes.[2]

These numbers are sobering, as are their implications. Serious microvascular, macrovascular, and neuropathic complications often develop that erode quality of life, increase costs of care, and contribute to ever-rising rates of diabetes-associated morbidity and mortality.

Among the most frequent complications is diabetic neuropathy, a collection of neuropathic syndromes that impair nerve function, with diverse clinical manifestations. The most common form — affecting approximately 30%-50% of diabetic patients[3] — is chronic sensorimotor distal symmetric polyneuropathy, or more simply diabetic peripheral neuropathy (DPN).[4] DPN is defined as "the presence of symptoms and/or signs in peripheral nerve function in people with diabetes after the exclusion of other causes."[5] Symptoms range from loss of sensation to deep, aching pain and primarily affect the feet and lower limbs. For 10%-20% of diabetic patients, pain is the primary symptom.[3,6] However, many patients have no apparent symptoms or are unaware of symptoms due to loss of sensation.[4]

DPN can interfere with activities of daily living and cause depression and anxiety.[7] When poorly managed, it may also lead to life-threatening complications of the feet, including ulceration, osteoarthropathy, and osteomyelitis. More than 60% of nontraumatic lower-limb amputations occur in patients with diabetes[1]; among diabetic patients, more than 80% of amputations follow a foot ulcer or injury.[4] These are stark consequences given that, if detected early, the progression of DPN can be prevented or at least delayed with treatment.

Yet DPN is frequently missed. Several studies suggest that mild DPN is underdiagnosed in approximately 60% of cases; severe DPN is overlooked in approximately 30% of cases.[8-10] A recent survey of patients with diabetes conducted by the American Diabetes Association (ADA) revealed that nearly two-thirds of respondents with symptoms of diabetic neuropathy believed the symptoms were associated with their diabetes — yet only 42% of patients with symptoms had been told by their doctor that diabetes was the cause, and only 25% had been diagnosed with diabetic neuropathy.[11] Missed diagnoses may mean unnecessary delays in treatment and progressive, irreversible nerve damage.

The intent of this brief review is to provide clinicians with information to help improve diagnosis and outcomes among patients with or at risk for DPN. Topics addressed include the underlying risk factors and pathophysiology of DPN, symptoms and clinical presentations of DPN, recommendations for screening, and current and emerging approaches to management and treatment once a diagnosis has been made.

Risk Factors and Pathophysiologic Mechanisms in DPN

Risk Factors

DPN has been associated with numerous risk factors, both modifiable and nonmodifiable (Table 1).[12-14] The duration of diabetes and degree of metabolic control are among the most important predictors of the development and severity of DPN.[13] Total hyperglycemic exposure, elevations in lipids, blood pressure, sex, age, height, and vitamin deficiencies have also been implicated. Vitamin B12 deficiency together with elevations in homocysteine, a metabolite involved in cellular metabolism and protein synthesis, may contribute to DPN; abnormal levels are considered toxic and may predict peripheral vascular disease and lower-limb ulcerations.[12,15] Metformin can elevate homocysteine and methylmalonic acid levels, which in turn may harm nerve cells.[15] Environmental factors, such as smoking and alcohol abuse, are also associated with DPN, as are family history and genetic factors.[16]

Table 1. Risk Factors for DPN

Modifiable Risk Factors	Nonmodifiable Risk Factors
Poor glycemic control (elevated A1c and glycemic variability)	Duration of diabetes
Obesity	Age
Hyperlipidemia/hypertriglyceridemia	Male sex
Hypertension	Height
Iatrogenic agents (eg, metformin, isoniazid)	Family history of neuropathic disease
Vitamin B12 deficiency/elevated homocysteine	Aldose reductase gene hyperactivity
Toxic agents (eg, nicotine or alcohol)	Angiotensin-converting enzyme genotype

A1c = glycated hemoglobin
Data from Ambrosch A, et al.[12]; Harati Y[13]; Tesfaye S, et al.[14]

Pathology

Many mechanisms have been proposed and investigated to explain the pathogenesis of diabetic neuropathy. Current thinking is that glucose dysregulation is central to a complex array of interrelated, interactive metabolic and vascular abnormalities that lead to nerve dysfunction and nerve cell loss (Table 2).[13,17,18]

Table 2. Metabolic and Vascular Factors Implicated in DPN Pathogenesis

Mechanism	Effect
Increased glucose flux through the polyol pathway	Accumulation of sorbitol, fructose, and myoinositol Reduction in sodium-potassium-ATPase Accumulation of nonenzymatic AGEs on nerve and/or vessel proteins
Oxidative stress Activation of redox-sensitive nuclear transcription factors Activation of protein kinase C	Increase in free radicals Increase in angiotensin 2 and endothelin Decrease in nitrous oxide Nerve hypoxia
Disturbances in metabolism of n-6 essential fatty acids and prostaglandins	Changes in nerve membrane structure Microvascular abnormalities Changes in blood flow
Reduced expression of nerve growth factor, neurotrophin-3, insulin-like growth factor	Deficits in neurotrophism Alterations in axonal transport Nerve cell death (apoptosis)
Immunologic processes	Formation of autoantibodies to vagal nerve, sympathetic ganglia, adrenal medulla Inflammatory changes

ATP = adenosine triphosphate; AGE = advanced glycation end products
Data from Harati Y[13]; Wooten K[17]; Ziegler D.[18]

Symptoms of DPN

Among patients with new or existing diabetes, clinicians need to be alert for signs and symptoms of DPN because early diagnosis and intervention may offset nerve cell damage and limit or delay pain, disability, and amputations.

Symptoms vary depending on which sensory neurons are affected[17] and may include pain, numbness, weakness, unsteadiness, and ataxia. When pain is present, it may manifest in diverse ways (Table 3), with most patients having multiple pain symptoms that are often worse at night.[17,19] Sometimes patients have difficulty describing their pain, which may contribute to misdiagnosis or underdiagnosis.[8,9,17,20]

Table 3. Symptoms Reported by Patients With Painful DPN

Persistent or paroxysmal pain independent of stimulus
Burning, shooting, throbbing
Tingling, pins and needles
Hot or cold sensations in the feet
Aching, cramping
Itching
Numbness
Stimulus-evoked pain
Hyperalgesia
Allodynia

Data from Daousi C, et al.[21]

Screening and Diagnosis

Because many patients lack symptoms or are unaware of them, symptoms are inadequate for detecting DPN. Early and routine screening is essential, and a wide range of simple tools are available and accepted for this purpose (Table 4). Ideally, clinicians should screen for DPN at the time of diabetes diagnosis and repeat screening at least once per year thereafter.[4] The ADA recommends that clinicians use multiple screening tests because combining 1 or more tests has > 87% sensitivity in detecting DPN.[4,22]

Table 4. Screening for DPN: Tests and Tools

Pain assessment questionnaires
Pinprick sensation
Vibration perception (using a 128-Hz tuning fork)
Pressure sensation (using a 10-g monofilament at the distal plantar aspect of both great toes and metatarsal joints)
Assessment of ankle deep tendon reflexes

Data from Boulton AJM, et al.[4]; American Diabetes Association[22]

The ADA also recommends at least 1 foot exam per year for all patients with diabetes; patients with confirmed DPN need more frequent foot exams. The exam should include careful inspection of both feet, palpation of the feet for pulses, evaluation of gait, and assessment of footwear to ensure proper size and fit.[22]

If screening identifies DPN, confirmation of diabetes as the cause is essential for determining approaches to treatment and management. Definitive diagnosis of DPN requires exclusion of hereditary, infectious, autoimmune, toxic or iatrogenic, and other possible etiologies (Table 5).

Table 5. Differential Diagnosis of Distal Symmetric Polyneuropathy

Etiology of Neuropathy	Syndrome or Condition
Congenital/familial	Charcot-Marie-Tooth
Traumatic	Entrapment syndromes (eg, carpel tunnel syndrome)
Metabolic or endocrine	Diabetes Uremia Pernicious anemia Vitamin B12, folate deficiency Hypothyroidism Acute intermittent porphyria
Inflammatory	Sarcoidosis Leprosy Lyme disease Human immunodeficiency virus
Autoimmune	Diabetes Phospholipid antibody syndrome Chronic inflammatory demyelinating polyneuropathy Multifocal motor neuropathy Guillain-Barre syndrome
Vascular	Diabetes Vasculitis
Neoplastic	Carcinoma-paraneoplastic syndromes Amyloid myeloma Reticulosis Leukemia Lymphoma
Toxic/iatrogenic	Alcohol Heavy metals Hydrocarbons Chemotherapeutic drugs Metformin

Reprinted from: Vinik AI, et al. Diabetic Neuropathy in Older Adults. *Clin Geriatr Med.* 2008;24(3):407-435. © 2008, with permission from Elsevier.[23]
Data from Boulton AJM, et al.[4]

Management of DPN

Current Pharmacologic Treatments
Pharmacologic management of diabetic neuropathy includes 2 approaches: treatments that slow the progression of neuropathy and treatments that provide symptom relief. No treatment has yet been identified that can reverse nerve cell damage or loss.

The most important step in preventing the onset and progression of DPN is to optimize glycemic control through diet and pharmacotherapy, including insulin as appropriate. Clinical trials have shown that attaining and maintaining near-normal blood glucose levels can delay progression of DPN[24,25]; furthermore, observational studies have found that both optimizing blood glucose levels and avoiding extreme glycemic fluctuations improve neuropathic symptoms.[4] Changes in lifestyle (smoking cessation, weight loss, reduction in blood pressure) and management of comorbid conditions, including depression and anxiety, have all been associated with improved outcomes related to health and quality of life in patients with DPN.[8,9]

Treatment of painful DPN involves primarily pharmacologic symptom management. Simple analgesics are usually inadequate. To date, only 2 agents -- duloxetine, a serotonin-norepinephrine reuptake inhibitor, and pregabalin, a calcium channel blocker — have formal approval from the United States Food and Drug Administration for managing painful DPN. The most recent guidelines on treatment of painful diabetic neuropathy, released in April 2011 by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation, have assigned a rating of "strong evidence, level A" to the use of pregabalin for treatment of diabetic neuropathic pain.[26]

A host of other treatments, including tricyclic antidepressants (TCAs) and other serotonin-norepinephrine reuptake inhibitors and anticonvulsants can also help manage pain and are included in current guidelines (Table 6).[4,26] In general, first-line treatment may involve TCAs, duloxetine, pregabalin, or gabapentin*. Clinicians should consider treatment costs and patient comorbidities when considering treatment choices.[19] Once treatment is underway, patients should be monitored to assess responsiveness and side effects and to optimize dosing. If initial treatment is inadequate, combinations of first-line treatments may be tried; if pain continues, opioids may provide relief. Topical agents such as capsaicin cream and isosorbide dinitrate spray can provide effective local pain control.

Any of these medications may be associated with adverse effects, and some have contraindications.[18,27] For example, TCAs have anticholinergic effects that may cause problems for patients with orthostasis, thyroid disease, impaired liver function, or other conditions; further, TCAS are contraindicated in patients with heart disease.[28] Opioids are associated with substantial side effects, such as sedation, and long-term use can lead to tolerance and dose escalations.[29] Clinicians and patients need to be aware of potential drug interactions. Drugs that may interfere with pain therapies for DPN include statins, beta blockers, sulfonylureas, levothyroxine, warfarin, and loop diuretics.[28]

Unfortunately, regardless of what treatment is used, most patients with painful diabetic neuropathy will experience only partial relief — no more than a 30%-50% reduction in pain.[8] As part of treatment selection, clinicians need to educate patients to set realistic expectations and balance optimal pain control with side effects. The challenge of managing painful DPN emphasizes the importance of prevention, as well as the need for further research to clarify pathologic mechanisms and identify optimal targets for treatment.

Table 6. Pharmacologic Treatments for Painful DPN

Class or Category	Agent (dose)*	Mechanisms of Action	Side Effects
Calcium channel modulators	Pregabalin (300-600 mg/d) Gabapentin (900-3600 mg/d)*	Bind to alpha-2-delta subunit on voltage-gated calcium channels; reduce neurotransmitter release in hyperexcited neurons	Pregabalin: dizziness, edema, somnolence Gabapentin: dizziness, somnolence, headache, diarrhea
Tricyclic antidepressants	Amitriptyline (25-100 mg/d)*	Inhibit reuptake of biogenic amines including norepinephrine and serotonin Impact on pain distinct from antidepressive effects	Dry mouth, somnolence, dizziness, constipation
Serotonin and norepinephrine reuptake inhibitors	Duloxetine (60-120 mg/d) Venlafaxine (75-225 mg/d)	Inhibit serotonin and norepinephrine reuptake, increase availability of 5-hydroxytryptamine and noradrenaline, which suppress pain impulses	Duloxetine: Nausea, headache, fatigue, constipation Venlafaxine: Somnolence, dyspepsia, insomnia, nausea, sweating
Opioids	Tramadol (210 mg mg/d) Oxycodone (mean 37 mg/d; max 120 mg/d) Morphine sulfate (titrated to 120 mg/d)	Stimulate mu-opioid receptors; alter pain perception in afferent pathways Tramadol also inhibits reuptake of norepinephrine	Constipation, somnolence, nausea, vomiting, dizziness; tolerance and hyperalgesia with chronic use
Topical treatments	Capsaicin cream (0.075% QID)	Depletes and prevents accumulation of substance P in peripheral sensory neurons	Skin irritation, cough
	Isosorbide dinitrate spray	Unknown; may help reverse nitric oxide depletion.	Palpitations, headaches, faintness
Other	Dextromethorphan, 400 mg/d	N-methyl-D-aspartate receptor antagonist	Dizziness, drowsiness, nausea, memory loss at high doses
	Sodium valproate, 500-1000 mg/d	Enhances action of gamma-amino butyric acid at postsynaptic receptor sites	Drowsiness, unsteadiness, nausea, decreased appetite

*Treatments assigned Evidence Level A or B in Evidence-based Guidelines for the Treatment of Painful Diabetic Neuropathy, released in April 2011 by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.[26]
Data from Bril V, et al[26]; Kochar DK, et al[30]; Yuen KCH, et al[31]; Zorn KE, et al[32]; Sang C, et al.[33]

Nonpharmacologic Treatments and Alternative Therapies
Limited response and unwanted side effects with pharmacologic treatment may drive many patients with painful DPN to seek alternative therapies. Several such therapies have been investigated in clinical trials. Percutaneous electrical nerve stimulation has been shown to dramatically reduce pain and also improves sleep.[34] Electrical spinal cord stimulation also relieves pain, even in the absence of pharmacologic agents, and its effect has been shown to endure for many years after implantation. But this method should be considered as a last resort because it is invasive and typically available only in specialist centers.[35,36] Studies of other alternative therapies, such as electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy, have shown no effect on painful diabetic neuropathy.[26]

Emerging Treatments for DPN
Numerous treatments are under investigation for DPN, many of which target specific pathologic mechanisms. Emerging treatments include aldose-reductase inhibitors, which block the rate-limiting enzyme in the polyol pathway, as well as alpha-lipoic acid and protein kinase C inhibitors, which act as antioxidants.[37] In clinical trials, alpha-lipoic acid improved neuropathic symptoms, but further study is needed.[38,39] Pilot studies with benfotiamine, a transketolase activator that reduces tissue accumulation of advanced glycation end products, have yielded improvements in neuropathy scores and decreases in reported pain levels.[40] In addition, recent investigations suggest that increasing levels of folate and B vitamins can normalize homocysteine levels in patients with DPN.[41] Dietary supplementation that incorporates both folic acid and vitamin B12 can reduce elevated serum homocysteine levels and improve neuropathic symptoms and quality of life, with few side effects.[20,42] Another option for local pain may be botulinum toxin. In a pilot study of patients with DPN, botulinum toxin injected intradermally in the feet provided significant pain reduction.[43] Additional, larger scale clinical trials are needed to verify findings for this and other emerging treatments.

Conclusions

As the incidence of diabetes cases continues to increase over the next several decades, DPN and other complications of diabetes are likely to become much more frequent. Ongoing and future research may identify treatments that more effectively improve symptoms of DPN, and perhaps halt or even reverse vascular and nerve damage. In the meantime, early and ongoing screening and careful glycemic control are paramount, since prevention of DPN is clearly preferable to the challenge of managing its symptoms.

*The FDA has not approved this medication for this use

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