



# Diabetic Neuropathy Collection: Treatment of Diabetic Neuropathy

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VG: Victoria Glasson (Managing Editor of *Diabetes Therapy*).

UA: Uazman Alam (Editorial Board Member of *Diabetes Therapy*).

This podcast is intended for medical professionals only.

VG: Hello, my name is Victoria Glasson and I am the editor for *Diabetes Therapy*. Today we are

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speaking to Dr Uazman Alam on the treatment of painful diabetic neuropathy.

UA: Hi Victoria, thanks for that introduction. My name is Uazman. I am a Senior Clinical Lecturer in Diabetes and Endocrinology and also an Honorary Consultant Physician. I work at the University of Liverpool and Aintree University Hospital, and I am also an Editorial Board member for *Diabetes Therapy*.

VG: So Uazman, how common is painful diabetic neuropathy?

UA: Painful diabetic neuropathy is a very common condition, it's highly prevalent. If we think about the number of patients we have with [type 2] diabetes [in the UK], 3.8 million [4.7 million for all types of diabetes in the UK] [1], around a third of these will have painful diabetic neuropathy. So this was primarily shown by the large study which was undertaken in the North West of England by Caroline Abbot which showed a third of all community-based patients had painful neuropathic symptoms [2]. However, with increasing severity, painful neuropathic symptoms increased and with the severest of diabetic neuropathy there was certainly around 60% of individuals having painful symptoms [2].

VG: And why do patients get pain in diabetes even when the clinical examination and tests such as nerve conduction studies are normal?

UA: So the earliest nerve fibres to be affected are the small nerve fibres [3]. These are the pain-generating nerve fibres. Now these are not routinely picked up on in nerve conduction studies

as nerve conduction studies target the larger fibres known as the A-beta fibres. In terms of a clinical examination these can be entirely normal but somebody can still have painful diabetic neuropathy. Essentially, pain is generated from the small nerve fibres which are not routinely detected by either [gross routine clinical examination or nerve conduction studies].

VG: What are the sensory symptoms of painful diabetic neuropathy?

UA: The symptoms can be broadly broken up into two categories. One is the negative sensory symptoms and the other is the positive sensory symptoms. So when I talk of negative sensory symptoms this includes the feeling of deadness and numbness, feeling that a person is wearing gloves and stockings. Positive symptoms are ones that tend to trouble the patients certainly a lot more; these include electric shock-like feelings, aching, tightness, hypersensitivity to touch, burning and prickling and all of these can cause a considerable amount of pain and discomfort [4].

VG: What should we be telling the patient before we start treatment for painful diabetic neuropathy?

UA: Certainly counselling is an important part of the treatment for painful diabetic neuropathy [5]. When I mean counselling that is the physician counsel the patient about what is expected and how the medication works and what they will need to do with the medication itself or how the medication should be taken. We certainly need to tell the patients that the pain relief is not immediate and anti-neuropathic agents do not work in the same way as a typical pain killer so the actual pain relief can take a number of weeks. Complete pain relief is also unlikely and really what we're hoping for is improvement in sleep and mood and also improvement in the patient's functioning as well. So really a good outcome is 50% pain relief [5]. The other important aspect is that patients should be aware that with most of the medications, this is particularly true of gabapentin, pregabalin and amitriptyline, that dose increases are generally required to obtain reasonable pain relief, so there needs to be an adequate dose titration.

VG: And what is the role of glycaemic control in the treatment of painful diabetic neuropathy?

UA: We should always aim to improve glycaemic control and cardiovascular risk covariates; however, there's no clear [definitive] evidence to suggest that improving glycaemic control in a person with painful diabetic neuropathy will improve the painful symptoms. However, saying that, we do need to ensure that the progression of neuropathy is halted or slowed down, so really treating their glycaemic control and other cardiovascular covariates [hyperlipidaemia, hypertriglyceridemia, hypertension, BMI, etc.] is really quite important. Now, on the other side of glycaemic control is something which was previously known as insulin neuritis or what we should call is treatment-induced neuropathy. This is when there is a rapid improvement in glycaemic control. Now, this can rarely cause pain and there's been a number of mechanisms which have been proposed. The one which is by Solomon Tesfaye [Sheffield, UK] [6] that suggests there may be A–V [arteriovenous] shunting in the peripheral nerve. But also a retrospective skin biopsy by Roy Freeman's group [Harvard, Boston] has shown that the majority of people with treatment-induced neuropathy had underlying diabetic retinopathy [7]. And it's possible that [underlying] angiopathy may promote this event so we do have to keep it in consideration that overly rapid improvement in glycaemic control, particularly over a short period of time, can induce neuropathic symptoms.

VG: Which medications are used in the treatment of painful diabetic neuropathy?

UA: So the typical medications which tend to be used and which are categorised as really being either first- or second-line are anticonvulsants and antidepressants. Within the anticonvulsant class, we have pregabalin and gabapentin and within the antidepressant class, we have duloxetine and the tricyclic antidepressant i.e. amitriptyline, although other tricyclic antidepressants have also been used.

VG: What are the differences in the international treatment guidelines for painful diabetic neuropathy?

UA: The international guidelines tend to agree that pregabalin, gabapentin and duloxetine and also tricyclics are either first- or

second-line in the treatment regime [5]. After this, there is some real divergence in what the recommendations are. But if we think about those four medications [classes], these are the ones that tend to be used as either first- or second-line. Now, one difference in the American Association of Neurology 2011 guidelines [8] recommended that pregabalin as first-line. Now, this is largely due to a technical aspect of the duloxetine studies in which some of them have a greater than 20% dropout and thus the level of evidence was not considered quite as strong [8]. The newer American Academy of Neurology guidelines are due and we'll see what their recommendations are.

VG: What are the differences in efficacy between gabapentin and tricyclic antidepressants?

UA: A study has looked at the differences between these two drugs but there's really no significant differences [in efficacy] found [9]. A meta-analysis of head-to-head trials comparing the results of gabapentin with two tricyclics did not show any difference and we know that pregabalin is similar efficacy to gabapentin in the most part, so there's no real difference so far that has been identified [9]. However, there is a study which is underway which is called OPTION-DM this is still underway and this is looking at combination therapy and treatment pathways with pregabalin, duloxetine and amitriptyline and certainly, this will shed more light on this question [10].

VG: And which medications in the drug class anticonvulsants are used in the treatment of diabetic retinopathy?

UA: So the two commonest anticonvulsants used and the ones with the greatest amount of evidence is gabapentin and pregabalin. So gabapentin has an effect. It's a GABAergic drug that actually binds to the alpha 2 delta subunit of voltage-gated calcium channels and it's thought to cause an inhibition through this pathway [11]. Pregabalin has a similar effect and also binds to the alpha 2 delta ligand [11]. The other two medications which were previously used in the anticonvulsant class were carbamazepine and phenytoin; however, they've really fallen out of favour now and they're rarely used. Carbamazepine tends only to be

used in trigeminal neuralgia. The other anticonvulsant which has found some favour, although the level of evidence is not so great, is sodium valproate and there was a recent Cochrane review [for neuropathic pain and fibromyalgia] which suggests that sodium valproate did not have any specific advantages over placebo [12].

VG: Which medications in the class of tricyclic antidepressants are used in the treatment of diabetic neuropathy?

UA: So the tricyclic antidepressant that's most commonly used is amitriptyline and one of the reasons for this is the trade-off with side effects that you get with the tricyclic antidepressants and the actual efficacy itself. In terms of the tricyclic antidepressant that has the lowest number needed to treat for benefit, this is actually imipramine [13]. [However, the quality of evidence for imipramine in neuropathic pain is considered poor [14].] However, imipramine does cause greater side effects than amitriptyline, so we tend to find that amitriptyline is more commonly used. Now amitriptyline generally requires a dose titration; patients are initiated on lower doses and subsequently a dose titration required to gain maximal efficacy. Overall, studies of tricyclics in diabetic neuropathy are small and are likely to have bias but the decades of use in painful diabetic neuropathy means that tricyclics have a robust standing within the international guidelines [15]. Interestingly, tricyclics may have some modulatory effects on the opioid receptor [16] but one thing we have to consider is their use is generally cautioned in people with cardiovascular disease and elderly people, and tricyclics need to be avoided in people with a prolonged QT or underlying cardiac arrhythmias.

VG: Which medications in the class of selective serotonin-norepinephrine inhibitors (SNRIs) are used in the treatment of painful diabetic neuropathy?

UA: The two medications commonly used within this class are duloxetine and venlafaxine. Duloxetine is certainly more commonly used and has more robust evidence, and duloxetine is the only one which actually has a

label for the use in painful diabetic neuropathy [15]. Other SNRIs are rarely used.

VG: And which medications in the class of serotonin reuptake inhibitor (SSRIs) are used in the treatment of painful diabetic neuropathy?

UA: Although studies have been done in this class, the evidence is not particularly great. However, we are aware that for people who have a low mood or are depressed and have painful neuropathic symptoms, if we can improve their depressive symptoms then certainly they will have an improvement in their painful neuropathy symptoms. But these don't really form a part of any international guidance and they're not routinely used. The two SSRIs which are used within clinical practice and have been looked at in painful neuropathy are paroxetine and citalopram, but I wouldn't recommend their use either as first-, second- or even third-line.

VG: So between pregabalin, gabapentin and duloxetine is any drug superior?

UA: So there's not a great deal of data on this; however, I must refer back to the COMBO-DN study [17]. So this was a study looking at combination therapy in terms of a combination of pregabalin and duloxetine vs high-dose monotherapy. But in the first instance, there was a run-in phase where people were either put on duloxetine or pregabalin [at standard doses]; duloxetine was at 60 mg per day and pregabalin was a total dose of 300 mg per day. And over the first 8 weeks, duloxetine had lower pain scores. Now I do emphasise that this was a secondary endpoint of the study but if we're thinking about head-to-head studies really this is the one probably with the most robust data where it did show that duloxetine was superior to pregabalin.

VG: Can non-steroidal anti-inflammatory drugs (NSAIDs) be used for painful diabetic neuropathy?

UA: NSAIDs is relatively ineffective for chronic painful diabetic neuropathy, so they do not form a part of the treatment guidelines.

VG: And what about opioids? Is morphine helpful?

UA: Well, we have to think about opioid class within the treatment of painful diabetic neuropathy as two separate areas. The first one

is what I call "opioid plus" medication; when I mean opioid plus these are medications that have an opioid effect plus an SNRI effect as well. Now there's two of these medications which can be very helpful: tramadol, which is a weak opioid and has a greater SNRI effect can certainly be used for breakthrough pain and I do tend to use this personally myself for people with breakthrough pain. Now there is a slight caution in people who are already on duloxetine as it can lower the seizure threshold [and serotonin syndrome] and there is a caution with the use of both of these in tandem [concurrently]. The other opioid of the opioid plus category, as I call it, is tapentadol, which is a strong opioid but has a weaker SNRI effect. Now both of these can be relatively effective in treating painful neuropathic symptoms. Morphine itself is of little benefit; the standard opioid medication does not have a great effect with painful diabetic neuropathy. There have been some studies of oxycodone but again it certainly doesn't form a part of the first- or second-line therapy that we should be using as third-line therapy is generally reserved as tramadol in some of the international guidelines.

VG: Are there any topical treatments that are used in the treatment of diabetic neuropathy, and which are the ones you use in clinical practice?

UA: So yes there are a number of topical treatments. So if we think about the topical treatments that I use in my own clinical practice, this includes a lidocaine patch, a 5% patch, and a glyceryl trinitrate (GTN) patch. Now there is some data that suggests that these can be helpful and I tend to use this in tandem with using the 5% lidocaine patch during the day and the GTN patch at night. The initial studies were actually done with isosorbide mononitrate spray which was sprayed on the feet but then subsequently Gerry Rayman showed that GTN was also effective in their study published in 2003 [18]. The other topical therapy which can be used in painful diabetic neuropathy is capsaicin cream. Now capsaicin cream needs to be applied multiple times a day and it can actually induce a burning feeling when it's applied. It has an effect via a TRPV1 receptor, also known as the chilli receptor, but that sort of limits its

use due to the number of times daily that the application is required and some of the side effects that go with it. There is, however, an 8% capsaicin patch which can be applied now; this is applied and then the repeat therapy is required a number of weeks later. But there's not a great deal of data really for painful diabetic neuropathy for this patch, but I am aware that there are some ongoing studies.

VG: And are there any other options for people who do not respond to oral and topical therapies?

UA: So for those with intractable pain who are really refractive to oral and to topical therapy, there is the IV lidocaine infusion. Now, this has previously been used in a study in 2006 which was published in the *Journal of Diabetes and its Complications* and was used in painful diabetic neuropathy [19]. So the dose is recommended at 5–7.5 mg per kg over a period of 4 h and then generally the therapy is repeated at a 10-weekly basis. And it's thought around half of people with intractable pain will have some kind of benefit from IV lidocaine and it's thought the mechanism can be twofold: one is to reduce the central sensitisation, and the other is modulation of sodium channels. But this, of course, requires treatment in a specialist setting and usually in a pain clinic with [continuous] ECG monitoring.

VG: What is the role of transcutaneous electrical nerve stimulation in the treatment of diabetic neuropathy?

UA: Transcutaneous electrical nerve stimulation has been used in some small studies; however, there's no definitive benefit from this, although if individuals did wish to try transcutaneous electric nerve stimulation it would offer no harm really as long as they were safe to do so [not contraindicated].

VG: Is there any role for spinal cord stimulator implants in the treatment of diabetic neuropathy?

UA: So spinal cord stimulators have been used for a number of years in a number of conditions but not so frequently in painful diabetic neuropathy. There have been studies which have also been undertaken here in Liverpool back in the 1990s by Solomon Tesfaye [20]. But certainly, there's no definitive efficacy

[demonstrated by a large randomised controlled trial] with spinal cord stimulators and really any referrals should be made to a pain specialist within tertiary centres.

VG: So are there any surgical options for painful diabetic neuropathy?

UA: A number of studies have looked at decompression surgery [21]. So this is, for instance, decompression of the lower limb nerves and also tarsal tunnel surgery. But really there is again no clear benefit from any of these procedures in improving painful diabetic neuropathy. Some of the studies that have been done have been flawed and it's certainly not recommended at the present moment.

VG: Is there any way for you to determine what medication people with painful diabetic neuropathy will respond to?

UA: So it's been suggested that the pain phenotype may determine what medication people may respond to. So, for instance, when I mean pain phenotype, in the paper published by Bouhassira in *Pain* 2014 [22], [it] was suggested that paraesthesia phenotype in diabetic neuropathy may respond to duloxetine. When I mean paraesthesia, these are individuals who have significant tingling in the limbs. A paroxysmal pain, those with paroxysms with pain may respond better to high dose pregabalin and this was published by Holbech in *Pain* 2015 [23]. And also, again, Bouhassira in *Pain* 2014 showed that combination therapy may actually be beneficial for moderate pain in painful diabetic neuropathy [22]. Now, when studies of therapeutics in painful diabetic neuropathy have been undertaken, they've not been stratified based on the underlying comorbidities. What I mean by this is, for instance, individuals will have a low mood or be depressed, or may have significant sleep disturbance. So how would this affect an individual with painful diabetic neuropathy starting on a therapy? And certainly, secondary analysis of randomised controlled trials [in non-specific pain] suggest that there's a case for duloxetine in people who are depressed [24] and in pain and pregabalin for people who have sleep disturbance and have painful diabetic neuropathy [25]. So in my own clinical practice, if somebody is depressed and has painful diabetic neuropathy, I will tend to

try them on duloxetine in the first instance or a tricyclic if the duloxetine is not an option. And if there's a significant sleep disturbance then certainly I will start them on pregabalin [for painful diabetic neuropathy].

VG: Can psychological therapies help in painful diabetic neuropathy?

UA: Certainly psychological therapies can be used and I certainly often refer some patients with more retractable pain, who are feeling they may have a more of a psychological aspect to the pain, to a psychologist. There's certainly pain management programs where people can be referred into and this is certainly an option for painful diabetic neuropathy.

VG: And what is the role of physical therapy in the treatment of painful diabetic neuropathy?

UA: So physical exercise may be of benefit, there is some trial data in regards to this [26, 27] but some degree of mild to moderate exercise, obviously depending on the patient's comorbidities and the status of their heart, can be considered. And It may be that they have a reduction of pain. Anecdotally, I've found that people who tend to be more active with painful diabetic neuropathy tend to have lower pain scores, but this is certainly anecdotal from my own clinical experience.

VG: Are there any novel therapies under development currently that you think are important to mention?

UA: The one novel therapy really that probably warrants mentioning is the Nav1.7 channel modulators or antagonists. Now, this is based on Nav1.7 channels which line the dorsal root ganglion and have a really important role in the modulation of pain [28]; and certainly, in painful diabetic neuropathy in a [putative] subset of individuals there's thought to be a gain of function in this channel [29]. However, this is really a class of medication which is currently being trialled mainly at phase 1 or 2 trials at present and is something that we need to just keep an eye on.

[For further review and for further reading, Dr Alam would suggest a paper which he published in *Clinical Therapeutics* 2018 by the name of "Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy" [4]. This

a detailed paper looking at the epidemiology and has detailed sections on pharmacotherapy.]

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