Clinical approach to the treatment of painful diabetic neuropathy

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Abstract: Painful neuropathy is a common and often progressive complication of diabetes. Patients frequently report symptoms of tingling, burning, lancinating pain, hyperesthesia, and allodynia. The natural history of the disease may vary from intermittent mild symptoms to severe chronic daily pain; the latter is often associated with diminished quality of life. There are a variety of pharmaceutical agents from different medicinal categories available for the symptomatic treatment of painful diabetic neuropathy, however selecting an agent is often challenging given the breadth of choices and lack of consistent guidelines. As a result, many patients remain untreated or undertreated. This article presents a practical clinical approach to the treatment of pain in diabetic neuropathy. Recommendations for first-, second-, and third-line medications are based on specific evidence for the treatment of painful diabetic neuropathy as well as safety, tolerability, drug interactions, and cost. Additional topics of discussion include breakthrough pain, opioid use, and topical therapies. This review does not comprehensively discuss all possible treatments for painful neuropathy, but provides a systematic approach designed to guide clinicians in tailoring therapies to the individual patient.

Keywords: diabetes, neuropathy, pain

Introduction

Painful neuropathy is a common, and at times debilitating, complication of diabetes. Approximately one in four people with diabetes may be affected by chronic neuropathic pain [Ziegler *et al.* 2009; Davies *et al.* 2006]. Patients often present with discomfort, typically starting in the distal feet, but progressing proximally over time. Patients may describe symptoms of numbness, tingling, burning, aching, electric shocks, or lancinating pains [Huizinga and Peltier, 2007]. Other sites that are often affected include the legs, arms, hands, and fingers. The pain may be constant or intermittent and there may be associated nocturnal worsening. Patients may also experience allodynia, when nonpainful stimuli are painful (commonly reported by patients when bed sheets become unbearably irritating), or hyperesthesia, when normally painful stimuli become excruciatingly painful.

There are multiple patterns of diabetic neuropathy. Sensory polyneuropathy is the most common; however sensory motor neuropathies, small fiber neuropathies, focal neuropathies, demyelinating (chronic inflammatory demyelinating polyneuropathy), and vasculitic (amyotrophic) neuropathies may also occur. Several mechanisms have been proposed to explain the effects of hyperglycemia on nerve fibers, including metabolic derangement, oxidative stress, and ischemia [Said, 2007]. A full review of the underlying pathogenesis and types of painful diabetic neuropathy is beyond the scope of this article.

Regardless of the type, the severity and clinical course may fluctuate for diabetic neuropathy. For many, the symptoms may become chronic and worsen with time. For some, however, there is gradual improvement and even resolution of pain [Gibbons and Freeman, 2010]. A decrease in painful symptoms may suggest nerve recovery; however progressive neuropathy may also cause loss of sensation, experienced as diminution of pain. Chronic painful diabetic neuropathy is known to impact many dimensions of patient quality of life, including mood, sleep, work, self-worth, and interpersonal relationships [Tolle *et al.* 2006; Schmader, 2002]. There are also significant individual and social costs from medications, health care visits, lost productivity,

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and adverse events, although the actual financial burden from painful diabetic neuropathy has not been differentiated from general diabetic neuropathy [Gordois *et al.* 2003].

Although treatment of pain is critical for quality of life, it must be considered only one aspect of overall care. Symptoms of neuropathy may not correlate with overall disease progression and therefore aggressive treatment of the underlying diabetes remains paramount. Control of glucose, blood pressure, lipids, and other microvascular risk factors are necessary for effective long-term management of this disease. The focus of this paper is the pharmacologic management of pain in patients with diabetic neuropathy.

There are many treatment options for pain in diabetic neuropathy but few medications have been vetted in large, randomized, placebo-controlled or head-to-head trials. Interpretation of the available data can be challenging because variables such as dosing, duration of treatment, and the definition of successful treatment may vary among studies. Guidelines and consensus statements are available, however these recommendations often differ and many medications have adverse effects or interactions with medications used to treat diabetes [Gore *et al.* 2008]. Additionally, there are older medications, such as tricyclic antidepressants, which are commonly used for painful diabetic neuropathy but have not been tested in randomized clinical trials for this condition. These older medications may be excluded from recommended guidelines using strict criteria despite their potential efficacy and utility. Given these variables, the actual implementation of treatment for painful diabetic neuropathy may prove daunting to clinicians and likely contributes to patients remaining untreated or undertreated [Van *et al.* 2009].

When to treat painful diabetic neuropathy

There are no clear guidelines for when to initiate symptomatic therapy, in part because treatment options do not alter the disease course. Patients' quality of life can be diminished by painful diabetic neuropathy through disruption of work and home productivity, mobility, mood, interpersonal relationships, and sleep [Argoff *et al.* 2006; Gore *et al.* 2006; Schmader, 2002; Galer *et al.* 2000]. Many of these variables are assessed in treatment trials for painful diabetic neuropathy and improve in parallel with the decrease in pain. Ideally, treatment should be initiated when patients identify that painful neuropathy is impairing activities of daily living and their quality of life. Successful management can decrease pain and improve quality of life.

There are a few treatment principles that can be helpful for both the patient and clinician when beginning therapy for neuropathic pain. First, it is important to establish realistic treatment goals and expectations because therapies typically do not result in complete resolution of symptoms. Second, medication dosing must be tailored to the individual patient. The goal of treatment is symptom resolution, not a specific medication dose. Thus it is important to use the lowest effective dose for an individual. Further titration can be considered, but must be weighed against an increased risk of side effects. Finally, there are some data to support drug combinations in painful diabetic neuropathy but it is generally advisable to avoid polypharmacy when possible.

Duration of treatment

The duration of time required for treatment is difficult to predict because the course of painful diabetic neuropathy is variable and the rate of pain recurrence is unknown [Huizinga and Peltier, 2007]. In many cases, the disease is both chronic and progressive. However, the pain may improve or resolve completely over time for some people [Benbow *et al.* 1994]. Decisions about cessation of treatment for pain can be of low importance when there are other medical issues, and may result in the continuation of unnecessary medication for long durations. If a patient is pain free for over 6 months, dose reduction or discontinuation is appropriate. If the patient has recurrence of symptoms during the taper or if the patient has noted recurrence of symptoms when missing a dose, then treatment should be continued (unless there are other contraindications). Of note, if a patient has persistent pain despite several adequate treatment trials, alternative etiologies for pain should always be considered.

Choices of treatment

We suggest a group of medications for use in first, second and third-line treatment of painful diabetic neuropathy. These recommendations are based on a combination of evidence of efficacy, safety, tolerability, drug interactions, and cost. Tiers are organized based on the available classes of literature and the quality of methodology employed. The list of reviewed medications is

not meant to be a compendium of all agents used to treat painful diabetic neuropathy, but rather a practical perspective of treatments with substantial available evidence.

Tier I medications are supported by evidence from three or more randomized clinical trials in patients with painful diabetic neuropathy, while tier II medications are supported by evidence from two randomized clinical trials in patients with this condition (see Table 1). Tier III medications are commonly used to treat painful diabetic neuropathy and are supported by evidence from two or more randomized clinical trials in patients with this condition but also have conflicting data reported. Tier III medications offer treatment options for patients who have either not tolerated or have been unable to take tier I and tier II drugs. A separate category of agents used for breakthrough pain as well as topical therapies are also described (see Table 1).

Details of each specific drug, including mechanisms of action, side effects, contraindications, pregnancy category, drug interactions with common diabetes medications, dosing, average monthly cost per drug, availability of generic formulations, and management in special populations (liver disease, renal disease, and geriatrics, including indications based on the revised Beers Criteria) are listed in the Supplemental Table (available online at http://tae.sagepub.com). The list of side effects includes common and serious symptoms but is not exhaustive. For each drug listed, the price is given in US dollars and is based on the generic formulation (when available). The price represents the average monthly cost of the average effective dose used for painful diabetic neuropathy.

There are many tricyclic antidepressants available with very similar mechanisms of action. The tier I recommendations, however, include only three: amitriptyline, imipramine, and desipramine. There is some evidence that other tricyclic antidepressants such as clomipramine may also be effective for painful diabetic neuropathy [Sindrup *et al.* 1990] but these medications were excluded based on the criteria described above. Many experts consider several of the tricyclic antidepressants to be interchangeable, therefore it may be reasonable to consider treatment with other tricyclic antidepressants if patients are unable to use the listed options or based on availability.

Comorbid depression

Many of the reviewed medications may worsen or trigger underlying mood disorders, including serious depression, and increase the risk of suicide in rare circumstances. Therefore, it is important to screen for depression and mood symptoms throughout treatment. Further details regarding initial and routine monitoring are listed in the Supplemental Table.

Some patients with underlying concomitant depression may experience an added benefit when treated with antidepressants. In most reviewed studies, however, depression was separated from improvement in pain as an endpoint, suggesting that improvement in pain is not secondary to a reduction in underlying depression alone. In addition, the doses used to treat depression may not be the same as those used for treatment of pain. The initial and average doses listed are for the treatment of painful diabetic neuropathy. Therefore, if patients are to be treated for both conditions with monotherapy, prescribers should review the guidelines on the doses for depression as well.

Opioids

The use of opioids for nonterminal chronic pain is controversial. Many treatment guidelines for painful diabetic neuropathy include opioids. While there are several studies examining this population that show short-term reductions in pain for those treated with oxycodone [Zin *et al.* 2010; Gimbel *et al.* 2003; Watson *et al.* 2003] there are no long-term studies evaluating the effect of opioids on the course, dosing, treatment response, or quality of life for these patients.

Unlike chronic pain from other conditions such as malignancy, neuropathic pain secondary to diabetes has a variable course. Initiating chronic opioid therapy in this population may leave patients vulnerable to progressive dose escalation over time and the associated risks of iatrogenic addiction. While actual rates of opioid addiction in patients with chronic nonterminal pain are difficult to assess, patients should not be exposed to this risk given that there are many other treatment options available. In addition, opioids may cause multiple side effects, including constipation, sweating abnormalities, hypogonadism [Daniell, 2002; Lee *et al.* 2002], and possible lowered immunity [Risdahl *et al.* 1998; Roy and

Table 1. Treatment recommendations.

Tier I	**Medications**	**Randomized placebo-controlled trials**	
• Supported by evidence from three or more randomized clinical trials in painful diabetic neuropathy • Safety profile • Tolerability • Number of significant drug interactions • Cost	**Tricyclic antidepressants:**		
	Amitriptyline	Max *et al.* (1987) Max *et al.* (1992) Bansal *et al.* (2009) Morello *et al.* (1999)	
	Desipramine	Max *et al.* (1991) Max *et al.* (1992) Sindrup (1990)	
	Imipramine	Sindrup *et al.* (1989) Kvinesdal *et al.* (1984) Sindrup *et al.* (2003)‡	
	Duloxetine	Goldstein *et al.* (2005) Raskin *et al.* (2005) Wernicke *et al.* (2006) Armstrong (2007)	
	Pregabalin	Rosenstock *et al.* (2004) Arezzo *et al.* (2008) Lesser *et al.* (2004) Richter *et al.* (2005) Freynhagen *et al.* (2005) Bansal *et al.* (2009) Tolle *et al.* (2008)	
	Gabapentin	Backonja *et al.* (1998) Backonja (1999) Morello *et al.* (1999) Sandercock *et al.* (2009)* Simpson (2001)	
Tier II	**Medications**	**Randomized placebo-controlled trials**	
• Supported by evidence from two or more randomized clinical trials in painful diabetic neuropathy • Safety profile • Tolerability • Number of significant drug interactions • Cost	Venlafaxine	Rowbotham *et al.* (2004)$ Kadiroglu *et al.* (2008) Sindrup *et al.* (2003)‡	
	Carbamazepine	Wilton (1974) Rull *et al.* (1969) Gomez-Perez *et al.* (1996)	
	Valproate	Kochar *et al.* (2002) Kochar *et al.* (2004) Agrawal *et al.* (2009)§	
Tier III	**Medications**	**Supportive randomized controlled trials**	**Conflicting randomized trials**
• Supported by evidence from two or more randomized clinical trials in painful diabetic neuropathy but with conflicting data • Safety profile • Tolerability • Number of significant	Lamotrigine	Eisenberg *et al.* (2001) Jose *et al.* (2007)‖	McCleane (1999)¶ Vinik *et al.* (2007)#
	Oxcarbazepine	Dogra *et al.* (2005)** Beydoun *et al.* (2006)‡‡	Grosskopf *et al.* (2006)$$

(continued)

Table 1. Continued.

drug interactions • Cost	Alpha lipoic acid	Ruhnau *et al.* (1999) Ziegler *et al.* (2006) Ametov *et al.* (2003)	Reljanovic *et al.* (1999) Ziegler *et al.* (1999)
Breakthrough pain	**Medications**	**Randomized placebo-controlled trials**	
• Supported by evidence from randomized clinical trials including painful diabetic neuropathy To be used as adjuvant therapies	Tramadol	Freeman *et al.* (2007)§§ Harati *et al.* (1998) Sindrup *et al.* (1999)	
	Lidocaine	Meier *et al.* (2003) ‖‖	
	Capsaicin	The Capsaicin Study Group (1991) Scheffler *et al.* (1991) Tandan *et al.* (1992)	

*This study examined use of gabapentin extended release which is not currently commercially available.
$This study examined use of venlafaxine extended release.
‡This was a randomized control trial of venlafaxine *versus* imipramine in neuropathic pain and included 15 patients with painful diabetic neuropathy.
§This was a double-blind randomized placebo-controlled trial in diabetic neuropathy which found that both valproate and a combination of valproate plus glyceryl trinitrate spray improved pain control.
|| This was a randomized control trial comparing lamotrigine with amytriptiline and placebo for the treatment of painful diabetic neuropathy.
¶This study examined lamotrigine dosing at 200 mg/day for neuropathic pain.
This study examined lamotrigine doses up to 400 mg/day.
**This study examined oxcarbazepine dosing at 1800 mg/day.
$$This study examined oxcarbazepine dosing at 1200 mg/day.
‡‡This study examined oxcarbazepine dosing at 600, 1200 and 1800 mg/day. The primary efficacy variable did not reach statistical significance, however patients with diabetic neuropathy who received the 1200 or 1800 mg/day dosing did have improvements in pain when compared with the placebo group and 600 mg/day dosing group.
§§This was a placebo-controlled trial examining tramadol with acetaminophen in the treatment of painful diabetic neuropathy.
‖‖ This was a placebo-controlled trial of lidocaine patches in the treatment of multiple types of painful neuropathy, including diabetic neuropathy.

Loh, 1996]. Such side effects are particularly problematic given this population's propensity for gastroparesis, hyperhidrosis, or hypohidrosis, erectile dysfunction (ED), and difficulties with wound healing. It is the authors' opinion that opioids should not be used for routine management of pain in patients with diabetic neuropathy unless all other avenues have been considered.

Breakthrough pain

Breakthrough pain is a common problem in the management of painful diabetic neuropathy. While over-the-counter analgesics including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen may be helpful, they may not offer sufficient pain control and may pose risks with chronic use. Patients with focal pain may benefit from the addition of topical therapies. Both lidocaine and capsaicin have been found to be effective in painful diabetic neuropathy. These topical therapies offer the advantage of fewer systemic side effects and drug interactions.

Lidocaine patches may be particularly helpful with localized pain and up to four patches of 5% lidocaine may be used for 12 h in a 24 h period [Argoff *et al.* 2004; Barbano *et al.* 2004]. In addition, for patients with inadequate pain control on monotherapy, lidocaine may act as an adjuvant, decreasing overall pain [Baron *et al.* 2009]. Lidocaine patches may also allow for reductions in total daily doses of oral

medications for patients who are unable to take higher doses of maintenance therapies. However, the significant cost for each patch may limit its utility.

Capsaicin 0.075% cream (recently approved for use in an 8% patch) is another topical treatment used for pain control in diabetic neuropathy. Capsaicin 0.075% cream reduces pain when used daily in this population [Forst *et al.* 2002; Tandan *et al.* 1992; The Capsaicin Study Group, 1991], but it causes degeneration of epidermal and dermal autonomic nerve fibers with use [Gibbons *et al.* 2010; Polydefkis *et al.* 2004; Nolano *et al.* 1999]. Cutaneous nerve fibers typically regenerate after capsaicin use is discontinued, however effects on patients with existing neuropathy are more pronounced and therefore caution is advised.

For patients with larger areas or greater intensities of breakthrough pain, topical treatments may not suffice. In this population, tramadol may be considered for breakthrough pain. Tramadol is a unique synthetic codeine-like compound. It appears to have some mild analgesic effects in its own right; however the majority of analgesia occurs secondary to metabolites which are demethylated through the cytochrome P (CYP) 450 2D6 system. Metabolites of tramadol have weak binding to the μ opioid receptor as well as serotonin and norepinephrine reuptake inhibition. Tramadol has been studied in patients with painful diabetic neuropathy [Freeman *et al.* 2007; Harati *et al.* 2000, 1998] and been found to reduce pain with daily use. Tramadol may be used for breakthrough pain if NSAIDs or acetaminophen are insufficient. If patients are using tramadol on a daily or almost daily basis, it may be necessary to switch to an alternative maintenance medication as this suggests that adequate pain control is not being achieved with the current regimen. Tramadol does have the potential to interact with most antidepressant medications, and care is required due to the potential duplicative serotonin and norepinephrine reuptake inhibition.

It should be noted that 7–10% of Caucasians are poor CYP 450 2D6 metabolizers and are therefore unable to metabolize tramadol [Kroemer and Eichelbaum, 1995]. In addition, there are many commonly used medications (including bupropion, fluoxetine, paroxetine, and metoclopramide) that inhibit the CYP 450 2D6 hepatic enzyme system [Armstrong *et al.* 2009; Laugesen *et al.* 2005]. These considerations should be taken into account when prescribing tramadol for breakthrough pain because patients may not achieve adequate analgesia when using tramadol despite dose escalations.

Alpha lipoic acid

Alpha lipoic acid is another tier III option in the treatment of painful diabetic neuropathy. Given its proposed antioxidant mechanism, it has been studied in several prospective placebo-controlled trials and found to reduce pain in patients with painful diabetic neuropathy [Burekovic *et al.* 2008; Ziegler *et al.* 2006; Ruhnau *et al.* 1999]. Both oral and intravenous formulations [Burekovic *et al.* 2008; Ziegler *et al.* 2004; Ametov *et al.* 2003] have shown reductions in pain. However, the ALADIN III study, a multicenter randomized controlled trial of intravenous followed by oral alpha lipoic acid over 7 months, did not demonstrate distinguishable effects from placebo [Ziegler *et al.* 1999]. There are also no studies examining the long-term effects of alpha lipoic acid. In addition, there are concerns that it may alter insulin sensitivity and glucose regulation, possibly potentiating diabetes medications (oral and insulin), causing hypoglycemia. Therefore, this medication remains a tier III drug which can be considered in patients whose condition has failed to respond to treatment or those who are unable to use other medications.

Clinical cases

The following four cases illustrate medical decision making in patients with painful diabetic neuropathy in different scenarios frequently encountered in clinical practice. These cases are intended to provide a framework for medication selection tailored to individual patient characteristics using the criteria described above.

Case 1

A 46-year-old man with a past medical history of type 2 diabetes presents to the office with complaints of persistent burning pain in his hands and feet. This has progressed over 2 years and he finds that the pain is interfering with his ability to fall asleep at night. Four years ago he was diagnosed with chronic kidney disease (CKD), now stage 3, and his current estimated glomerular filtration rate (eGFR) is 40 ml/min. His past medical history is otherwise remarkable for significant obesity and occasional ED.

This patient is describing persistent painful neuropathy which warrants treatment. All of the tier I and II medications should be used with caution in patients with renal insufficiency. Of the tier I drugs, only duloxetine explicitly should not be used in patients with a creatinine clearance (CrCl) of less than 30. This patient's CrCl (or surrogate eGFR) is still above 30; however, because other medication options are available, duloxetine should be avoided if possible. Of the remaining tier I medications, a tricyclic antidepressant, pregabalin, or gabapentin could be considered. Both gabapentin and pregabalin are excreted renally, and would require dose reduction.

Of the choices, a tricyclic antidepressant is the most cost effective. Desipramine is the tricyclic antidepressant with both the lowest muscarinic (cholinergic) receptor affinity and the lowest risk of adverse events. Finally, of the choices described, it has a lower incidence of sexual side effects compared with other tricyclic antidepressants, but still will need to be monitored.

Patients should have a baseline ECG if there is prior cardiac history or they are older than 40 years. This is to exclude cardiac diseases (including recent myocardial infarction [MI], heart failure, arrhythmias, and prolonged corrected QT interval) which are contraindications for use. Initial dosing should start at 10–25 mg at bedtime and be titrated by 10–25 mg per week [Max *et al.* 1992, 1991] to efficacy or a dose of 100 mg/day. During treatment, patients should be routinely monitored for depression. Discontinuation should be done gradually with a taper over several weeks.

Case 2

A 59-year-old woman with type 2 diabetes presents to an outpatient clinic with complaints of numbness and pins and needles in her feet for the past 2 years. Over the last 4 months, the symptoms have become increasingly bothersome and she has noted that her mood is more irritable. She has been treated in the past with gabapentin 300 mg taken every night without effect. Her past medical history is remarkable for liver disease secondary to alcohol use with subsequent diabetes and thrombocytopenia. She has also had both hepatic encephalopathy and hepatorenal syndrome in the past. She no longer has difficulties with alcohol abuse.

This patient's parethesias have been persistent and may also be influencing her mood, therefore symptomatic treatment may help improve her quality of life. Given her history of cirrhosis, tricyclic antidepressants and duloxetine should be used with caution. The only tier I medications without a contraindication in liver disease are pregabalin and gabapentin. She has tried gabapentin in the past without effect, however only at low doses once per day. Pregabalin is an alternative tier I option but is more expensive. As both gabapentin and pregabalin have similar mechanisms of action, it is therefore reasonable to repeat a trial of gabapentin first.

The starting dose for gabapentin is 300 mg daily (or divided three times a day) and this dose can be titrated as tolerated to symptomatic relief, or to 1200 mg three times a day. No baseline monitoring is necessary, however patients treated with gabapentin should be periodically monitored for mood symptoms and worsening depression or suicidality. Common side effects include dizziness and somnolence; Stevens–Johnson syndrome is a rare complication.

The patient returns for follow up after 4 months of treatment. Her symptoms have improved since taking gabapentin 800 mg three times a day, however at times she has breakthrough pain characterized by a stabbing sensation in her feet extending to her ankles. This occurs most often after she has been exercising and she finds that these episodes limit her ability to continue her activity. Aside from the breakthrough pain, her symptoms are generally tolerable. She has tried both acetaminophen and NSAIDs without relief and is interested in exploring treatment for breakthrough pain.

Given the larger surface area of her breakthrough pain, topical lidocaine or capsaicin patches may be difficult to apply and may not adequately cover the region involved. Therefore, tramadol may be considered for the management of breakthrough pain. Patients should be counseled that this medication is not meant for daily therapy and should be reserved for times when pain is exacerbated or function limited. Given her liver disease, her dosing should not exceed 50 mg every 12 h of the immediate release formulation. During treatment, she should be routinely monitored for adequate pain control as well as signs of tolerance and abuse.

Case 3

An 82-year-old man with a longstanding history of type 2 diabetes mellitus was referred for treatment of chronic pain. The pain is mostly in his feet below the ankles and he describes it as both lancinating and searing. He is unable to tolerate even light touch on his feet and as a result he has decreased mobility. His past medical history is significant for a prior MI and chronic venous stasis in the lower extremities. Before leaving the office, his daughter expresses concerns that her father forgets to take his medications some times.

This patient has symptoms of hyperesthesia and allodynia which are causing him pain and limiting his mobility. Based on the revised Beers criteria [Fick *et al.* 2003], tricyclic antidepressants should be avoided given this patient's age. Either duloxetine, pregabalin, or gabapentin could therefore be considered as tier I options. Duloxetine has the advantage of once daily dosing, which may be helpful in patients for whom medication compliance is difficult. It is not associated with peripheral edema, which may be rarely seen with pregabalin and gabapentin. It should be noted, however, that duloxetine is more expensive than the remaining choices.

Before starting treatment, patients should be screened for underlying renal insufficiency with a serum chemistry because dosage reduction may be necessary in mild to moderate renal impairment. Liver functions should also be checked because duloxetine should not be used in hepatic impairment. Some patients with diabetes treated with duloxetine experience increases in both serum glucose and glycated hemoglobin (HbA_{1c} or A1C) during treatment, therefore both should be assessed at baseline. If during treatment these results increase without other cause, cessation of duloxetine may be necessary. Patients should also be screened for hypertension and depression both prior to and during treatment. The initial dose is 60 mg/day, however in the elderly, initiation with a lower dose of 20 or 30 mg/day is appropriate. The dose may then be gradually titrated as tolerated to a goal dose of 60 mg/day. This remains the average effective dose for most patients. Lower doses can be used to initiate therapy if necessary but higher doses have not been found to be more effective.

Case 4

A 28-year-old woman with a past medical history of type I diabetes presents to the office for treatment of a burning sensation in her toes. This symptom started about 4 months ago and is almost constant, but is worse in the evening. At night, contact with the sheets is very painful and she must sleep with her feet hanging off the end of the bed to avoid touching anything. Her past medical history is otherwise remarkable for depression but she is not currently on medication for this condition.

This patient's symptoms are consistent with mild diabetic neuropathy. She does not have clear contraindications for any medications, therefore treatment with a tricyclic antidepressant would be reasonable and the most cost effective tier I choice. Given her age and lack of other vascular history, a baseline ECG is not necessary. In this class of medications, amitriptyline is the most studied in controlled trials for painful diabetic neuropathy and has repeatedly been found to be effective [Bansal *et al.* 2009; Morello *et al.* 1999; Max *et al.* 1992, 1987] . This medication is pregnancy category C, therefore the patient should be counseled about this prior to treatment. The initial dose of amitriptyline is 10–25 mg every night, which can be titrated by increasing 10–25 mg per week (based on symptomatic response and tolerability). The average effective dose is 100 mg/day, but many patients achieve relief with lower doses. Amitriptyline has the highest affinity for the muscarinic (cholinergic) receptors [Duby *et al.* 2004] of the tricyclic antidepressants, which may limit tolerability, especially at higher doses. During treatment, this patient should be routinely screened for possible worsening depression and other mood symptoms.

Two months after starting amitriptyline the patient returns for follow up. She is currently taking 75 mg/day and overall her symptoms have improved. She was unable to tolerate a higher dose due to dry mouth and dizziness. She now reports allodynia in her toes. This symptom is intermittent and occurs primarily at night when she has the blanket or sheets on her feet. At times the discomfort causes her to have difficulty falling asleep.

This patient may benefit from a topical therapy as she has been unable to tolerate higher doses of amitriptyline. Her symptoms are episodic, and only involve a small surface area. Lidocaine patches applied to the painful portions of feet in the evening as needed may be helpful. The patches are to be applied for 12 h on and then

12 h off. Most patients experience improvement in symptoms after the first week of treatment. Topical therapy in this patient avoids potential systemic polypharmacy and drug interactions. It should be noted, however, that lidocaine patches can be quite costly and this issue should be discussed with the patient prior to initiating therapy.

Conclusion

Treatment of painful diabetic neuropathy can prove challenging for both patients and clinicians. There are multiple different guidelines available, however often with conflicting information. In addition, the quality of available studies varies, sometimes with small numbers and differing endpoints. As new drugs are tested in the coming years, these issues will likely persist, making medication selection increasingly complex. Therefore, developing a treatment strategy which incorporates the available literature on efficacy, dosing, side effects, contraindications, drug interactions, and cost is necessary to guide clinicians in developing tailored treatment for the individual patient. This is not a comprehensive review of all possible treatments, but rather a detailed, stepwise discussion of when and how to use some of the available drugs for painful diabetic neuropathy. The treatment of symptoms must occur in conjunction with aggressive treatment of diabetes and other comorbid risk factors to reduce progression of the neuropathy. Future reviews will be necessary to incorporate emerging data from new studies and treatment options.

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Conflict of interest statement

The authors report no conflicts of interest.

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Supplemental Table. Medication details.

Tier I	**Tricyclic antidepressants**			
Side effects				
Common	Dry mouth; constipation; dizziness/orthostatic hypotension; urinary retention; sedation; blurred vision; weight loss (imipramine, desipramine); weight gain (amitriptyline, imipramine, desipramine); sexual side effects (imipramine)		**Mechanism of action:** SNRI	
			$T_{1/2}$	
Serious	Cardiac dysrhythmia; myocardial infarction; worsening depression and suicidality; may alter glucose regulation (imipramine, desipramine)		Amitriptyline	9–27 h
Contraindications	MAOI use within 2 weeks; cardiac history (including recent MI, heart failure, and arrhythmias, prolonged corrected QT); glaucoma		Imipramine	6–18 h
			Desipramine	7–60 h
Dosing			**Pregnancy category:** C–D*	
Starting	Amitriptyline	10–25 mg/day	**Cost**	
	Imipramine	10–25 mg/day	Amitriptyline	$
	Desipramine	10–25 mg/day		
Average effective	Amitriptyline	100 mg/day	Imipramine	$
	Imipramine	150 mg/day		
	Desipramine	100 mg/day		
Titration	Weekly as tolerated		Desipramine	$$
Monitoring			**Generic available:** Y	
Baseline	ECG for patients with history if cardiac disease or age >40			
Periodic	Periodic screening for depression			
Special populations				
Renal disease	Use with caution		**DM medication drug–drug Interactions:** N	
Liver disease	Use with caution	Hepatic metabolism		
Geriatrics	High risk (imipramine max dose should not exceed 100 mg/day in elderly patients)			

Tier I	**Duloxetine**	
Side effects		
Common	Nausea; somnolence; dizziness; loss of appetite; constipation; may lower serum glucose; weight loss; weight gain; sexual side effects	**Mechanism of action:** SNRI
Serious	Abnormal bleeding; hepatotoxicity; worsening depression/suicidality; serotonin syndrome	**$T_{1/2}$:** 12 h
Contraindications	Uncontrolled narrow-angle glaucoma; concurrent treatment MAOI	**Pregnancy category:** C
Dosing		**Cost:** $$$$
Starting	20–60 mg/day	
Average effective	60 mg/day	
Titration	As tolerated	
Monitoring		**Generic available:** N
Baseline	Blood work: chemistry; liver function tests and glycated hemoglobin (HbA_{1C} or A1C); screening for hypertension and depression	
Periodic	Periodic screening for depression	

(continued)

Supplemental Table. Continued.

Special populations			
Renal disease	Dosage reduction may be required for mild to moderate renal impairment Not recommended for CrCl < 30 ml/min or ESRD		**DM medication drug–drug Interactions:** N
Liver disease	Hepatic metabolism	Not recommended for use in hepatic impairment	
Geriatrics	No special dosing recommended		

Tier I	**Pregabalin**		
Side effects			
Common	Dizziness; somnolence; peripheral edema; constipation; xerostomia; headache; weight gain		**Mechanism of action:** acts on voltage-gated calcium channels
Serious	Angioedema		
Contraindications	Use with caution in patients with congestive heart failure		**$T_{1/2}$:** 6.3 h
Dosing			**Pregnancy category:** C
Starting	50 mg three times a day		
Average effective	100 mg three times a day		**Cost:** $$
Titration	Can be rapidly titrated within a week		
Monitoring			**Generic available:** N
Baseline	N/A		
Periodic	Periodic screening for depression		
Special populations			
Renal disease	–		**DM medication drug–drug interactions:** Y May increase fluid retention in patients concomitantly treated with thiazolidinedione
Liver disease	Use with caution	Reduce total daily dose in proportion to renal impairment	
Geriatrics	No special dosing recommended		

Tier I	**Gabapentin**	
Side effects		
Common	Dizziness; somnolence; weight gain; sexual side effects	**Mechanism of action:** unknown‡
Serious	Stevens–Johnson syndrome; worsening depression/suicidality	**$T_{1/2}$:** 5–7 h
Contraindications		**Pregnancy category:** C
Dosing		**Cost:** $$
Starting	300 mg/day every night or divided into three times a day	
Average effective	800 mg three times a day (maximum dose of 3600 mg/day divided over three times a day)	
Titration	As tolerated	
Monitoring		**Generic available:** Y
Baseline	N/A	
Periodic	Periodic screening for depression	

(continued)

Supplemental Table. Continued.

Special populations		
Renal disease	Reduce total daily dose in proportion to renal impairment	**DM medication drug–drug interactions:** N
Liver disease	–	
Geriatrics	–	

Tier II	**Venlafaxine**	
Side effects		
Common	Nausea; somnolence; headache; weight loss; sexual side effects	**Mechanism of action:** SNRI
Serious	Hyponatremia; gastrointestinal hemorrhage; bleeding abnormalities; neuroleptic malignant syndrome; serotonin syndrome; worsening depression/suicidality	**$T_{1/2}$:** 5 ± 2 h
Contraindications	Recent MAOI use	**Pregnancy category:** C
Dosing		**Cost:** $$$
Starting	Venlafaxine immediate release 37.5 mg twice a day or venlafaxine extended release 75 mg/day	
Average effective	Venlafaxine immediate release 112.5 mg twice a day or venlafaxine extended release 150–225 mg/day	
Titration	As tolerated	
Monitoring		**Generic available:** Y
Baseline	Serum cholesterol; screening for hypertension and depression	
Periodic	Periodic screening for depression; blood pressure monitoring	
Special populations		
Renal disease	Use with caution: Reduce total daily dose by 25% in mild to moderate renal impairment (CrCl 10–70 ml/min); reduce total daily dose by 50% if on hemodialysis	**DM medication drug–drug interactions:** N
Liver disease	Hepatic metabolism: Reduce total daily dose by 50% in mild to moderate renal impairment	
Geriatrics	No special dosing recommended but may benefit from lower initial dosing	

Tier II	**Carbamazepine**	
Side effects		
Common	Dizziness; drowsiness; dry mouth; ataxia; nausea; vomiting; hyponatremia; pancytopenia; abnormal liver function; sexual side effects	**Mechanism of action:** inhibition of voltage-dependent sodium channels
Serious	Dysrhythmia; congestive heart failure; Stevens–Johnson syndrome; toxic epidermal necrolysis; nephrotoxicity; hypocalcemia, hyponatremia; blood dyscrasia including aplastic anemia	**$T_{1/2}$:** 12–17 h
Contraindications	Blood dyscrasias; dermatologic reactions; presence of HLA-B*1502 allele is a contraindication, however guidelines for routine screening of Asian patients has not been established	**Pregnancy category:** D
Dosing		**Cost:** $$$
Starting	200 mg/day	
Average effective	300 mg/day or twice a day	
Titration	Over 2 weeks	

(continued)

Supplemental Table. Continued.

Monitoring			**Generic available:** Y
Baseline	Complete blood count; liver function tests; chemistry; thyroid function tests; screening for depression		
Periodic	Complete blood count; liver function tests; chemistry; thyroid function tests; carbamazepine levels§; screening for depression		**DM medication drug–drug interactions:** Y Concurrent use of carbamazepine and repaglinide may cause lower serum repaglinide concentrations
Special populations			
Renal disease	Use with caution	No dose adjustment recommended	
Liver disease	Hepatic metabolism; Use with caution	No dose adjustment recommended	
Geriatrics	No special dosing recommended		

Tier II	**Valproate**		
Side effects			
Common	Headache; somnolence; dizziness; nausea; dyspepsia; abdominal pain; tremor; hair loss; weight loss; weight gain		**Mechanism of action:** increases effects at GABA receptor
Serious	Pancreatitis; thrombocytopenia; hepatic failure		$T_{1/2}$: 9–16 h
Contraindications	Hepatic failure; pancreatitis; urea cycle disorders		**Pregnancy category:** D‖
Dosing			**Cost:** $$
Starting	500 mg/day or 300 mg twice a day		
Average effective	500–600 mg twice a day		
Titration	As tolerated		
Monitoring			**Generic available:** Y
Baseline	Liver function tests; complete blood count; prothrombin time; partial thromboplastin time; ammonia; screening for depression		
Periodic	Liver function tests; complete blood count; prothrombin time; partial thromboplastin time; ammonia; valproate levels; screening for depression		
Special populations			
Renal disease	No significant effect on metabolism, however renal disease may influence protein binding and clearance		**DM medication drug–drug interactions:** N
Liver disease	Hepatic metabolism	Use with caution Dose reduction required Contraindicated in severe liver disease	
Geriatrics	No special dosing recommended but may benefit from lower initial dosing		

Tier III	**Oxcarbazepine**		
Side effects			
Common	Abdominal pain; nausea; vomiting; ataxia; dizziness; headache; nystagmus; somnolence; tremor; vertigo; diplopia; rhinitis; fatigue; weight loss; weight gain		**Mechanism of action:** oxcarbazepine and its active metabolite monohydroxy metabolite block voltage-sensitive sodium channels and modulate voltage-activated calcium channels
Serious	Hyponatremia; Stevens–Johnson syndrome; toxic epidermal necrolysis; angioedema		
Contraindications	–		$T_{1/2}$: oxcarbazepine 2 h; monohydroxy metabolite (active metabolite) 9 h
Dosing			
Starting	300 mg/day		**Pregnancy category:** C
Average effective	1200 mg/day divided into twice or three times a day dosing		**Cost:** $$$$
Titration	Weekly titration to twice a day dosing Slow titration for patients with CrCl < 30 ml/min		

[continued]

Supplemental Table. Continued.

Monitoring			**Generic available:** Y
Baseline	Serum sodium		
Periodic	Serum sodium; periodic screening for depression		
Special populations			
Renal disease	For CrCl <30 ml/min: initial dose should be half the starting dose with slow titration		**DM medication drug–drug interactions:** N
Liver disease	Hepatic metabolism	No dose adjustment recommended for mild to moderate impairment. No data available for severe liver disease	
Geriatrics	No special dosing recommended		

Tier III	**Lamotrigine**		
Side effects			
Common	Nausea; abdominal pain; headache; drowsiness; dizziness; weight loss		**Mechanism of action:** stabilization of neural membranes through voltage-gated sodium channels; and inhibition of presynaptic release of glutamate
Serious	Stevens–Johnson syndrome; toxic epidermal necrolysis; hepatic failure; anemia/thrombocytopenia/pancytopenia		
Contraindications	–		
Dosing			
Starting	25 mg/day		**$T_{1/2}$:** 25–33 h
Average effective	150–200 mg twice a day		**Pregnancy category:** C
Titration	Slow; 25 mg increase per week. More rapid titration is contraindicated because of concern for Stevens–Johnson syndrome		**Cost:** $$$$$
Monitoring			**Generic available:** Y
Baseline	N/A		
Periodic	Periodic screening for depression and rash		
Special populations			
Renal disease	Renal metabolism	Use with caution; dosage reduction may be required	**DM medication drug–drug interactions:** N
Liver disease	Hepatic metabolism	Use with caution; dosage reduction may be required	
Geriatrics	No special dosing recommended		

Tier III	**Alpha lipoic acid**	
Side effects		
Common	Paresthesias; muscle cramps; platelet dysfunction; headache; rash; nausea; vomiting; vertigo	**Mechanism of action:** antioxidant
Serious	Hypoglycemia	**$T_{1/2}$:** 30 min
Contraindications	Unknown	**Pregnancy category:** unknown
Dosing		**Cost¶:** N/A
Starting	300 mg twice a day (or 200 mg three times a day)	
Average effective	600 mg once daily or divided twice a day	
Titration	N/A	
Monitoring		**Generic available:** N/A
Baseline	Unknown	
Periodic	Periodic screening for depression	

(continued)

Supplemental Table. Continued.

Special populations		
Renal disease	Unknown	**DM medication drug–drug interactions:** unknown; may interact with insulin and oral hypoglycemics
Liver disease	Unknown	
Geriatrics	Unknown	

Breakthrough pain	**Lidocaine patch**	
Side effects		
Common	Local skin irritation; itching; edema; rash; urticaria; blisters; angioedema	**Mechanism of action:** decreased neuronal membrane permeability to sodium ions
Serious	Allergic/anaphylactoid reaction	
Contraindications	Skin breakdown in area of application	
Dosing		
Starting	One patch applied to painful area. Patch may remain in place for up to 12 h in any 24 h period	**$T_{1/2}$:** unknown#
Average effective	As above	**Pregnancy category:** B
Titration	N/A	**Cost**:** $$$$$
Monitoring		**Generic available:** N
Baseline	N/A	
Periodic	Check skin for reactions at site of patch	
Special populations		
Renal disease	No special dosing recommended	**DM medication drug–drug interactions:** N
Liver disease	No special dosing recommended	
Geriatrics	No special dosing recommended	

Breakthrough pain	**Capsaicin**	
Side effects		
Common	At site of application: itching; burning; stinging; erythema; cough; nausea	**Mechanism of action:** depletes stores of peripheral nerve substance P and prevents reaccumulation
Serious	Hypertension	
Contraindications	Skin breakdown in area of application	
Dosing		**$T_{1/2}$:** 1.64 h
Starting	N/A	**Pregnancy category:** C
Average effective	0.075% capsaicin patch or cream applied 3–4 times per day PRN	**Cost‡‡:** $–$$$
Titration	N/A	
Monitoring		**Generic available:** Y
Baseline	N/A	
Periodic	Check skin for reactions at site of patch	

(continued)

Supplemental Table. Continued.

Special populations		
Renal disease	No special dosing recommended	**DM medication drug–drug interactions:** N
Liver disease	No special dosing recommended	
Geriatrics	No special dosing recommended	

Breakthrough pain	**Tramadol**		
Side effects			
Common	Flushing; pruritus; constipation; nausea; vomiting; dyspepsia; xerostomia; dizziness; headache; somnolence; insomnia; weight loss; sexual side effects		**Mechanism of action:** tramadol and its active metabolite bind to central μ-opiate receptors and inhibit ascending pain pathways; also inhibits serotonin and norepinephrine reuptake.
Serious	Dyspnea; respiratory depression; myocardial infarction; pancreatitis; seizure; serotonin syndrome		
Contraindications	Acute intoxication with CNS depressants (alcohol, hypnotics, opioids, or psychotropic drugs)		
Dosing			**$T_{1/2}$:§§** tramadol: ~6–8 h; active metabolite: 7–9 h
Starting	50 mg/day PRN		
Average effective	50–200 mg/day divided twice daily PRN		**Pregnancy category:** C
Titration	To be used PRN		**Cost:** $||||
Monitoring			**Generic available:** Y
Baseline	N/A		
Periodic	Monitor for tolerance and abuse		
Special populations			
Renal disease	For CrCl < 30 ml/min: – immediate release: 50–100 mg every 12 h; maximum: 200 mg/day – extended release should not be used		**DM medication drug–drug interactions:** N
Liver disease	Hepatic metabolism	For cirrhosis: – immediate release: 50 mg every 12 h – extended release should not be used	
Geriatrics	Use with caution	>65 years: start with lower doses >75 years: do not exceed 300 mg/day of immediate release formulation	

*Imipramine is pregnancy category D.

‡May act on voltage-gated calcium channels and impact the release of excitatory neurotransmitters.

§Owing to hepatic autoinduction, serum levels must be monitored until stable.

|| Known teratogen.

¶Prices vary based on distributors.

#Half-life of topical lidocaine is not known. It is not clear if it is metabolized in the skin. The half-life of intravenous lidocaine is 1.5–2.5 hours.

**Cost listed is for 30 patches of Lidoderm.

‡‡Cost based on price per tube of 0.075% capsaicin cream or packages of four patches used four times a day although this is not the recommended dosing.

§§ T1/2: prolonged in elderly, hepatic and renal impairment.

|||| Listed cost is for 90 tablets of 50 mg tramadol immediate release.

Key for costs: $, US$0–50; $$, US$51–100; $$$, US$101–150; $$$$, US$151–200; $$$$$, >US$201.

CrCl, creatinine clearance; DM, diabetes mellitus; ESRD, end-stage renal disease; MAOI, monoamine oxidase inhibitors; MI, myocardial infarction; PRN, pro re nata; SNRI, serotonin–norepinephrine reuptake inhibitor.