The use of topical analgesics in the management of painful diabetic neuropathy

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Painful diabetic neuropathy (PDN) affects up to half of patients with diabetes and is a major cause of functional impairment and increased mortality. Its clinical manifestations include sensations such as burning, stabbing and tingling and/or loss of sensation, and it increases the risk for injuries and foot ulceration. Oral pharmacological therapy is the standard approach to management. It is effective in some patients, but its use is limited due to unfavourable side-effect profiles, limited response rates and drug interactions. Increasing evidence of the localized, non-systemic treatment approach of topical analgesics aims to overcome these obstacles and provide valuable, efficacious and safe management of PDN. This article reviews the rapidly expanding field of topical analgesia in managing PDN.

Oral pharmacological therapy is the traditional approach for the management of painful diabetic neuropathy (PDN). Current guidelines recommend starting with medications initially developed for the treatment of seizures and depression (Box 1; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013).

Opioids, such as morphine and oxycodone, are usually considered when treatment failure occurs with first-line therapies, but are used with caution due to the risk of dependence and dose-related side-effects. Despite its established place in therapy, the use of oral medications imposes obstacles to many patients with PDN, as management of their pain is frequently complicated by multiple co-morbidities and polypharmacy. Even so, evidence shows that only partial pain reduction is achieved in patients with PDN treated with oral pharmacotherapy (Krein et al, 2005). For these reasons, patients suffering from painful diabetic neuropathy are often ideal candidates for topical analgesics.

Box 1 summarizes recommendations for screening and treatment of PDN.

Patients with PDN often have multiple chronic conditions, organ dysfunction (renal, hepatic) and other risk factors (cardiac, gastro-intestinal) that put them at risk of drug interactions and adverse events (Wild et al, 2004). Topical analgesics deliver medication directly to the site of pain, providing the same therapeutic benefit as their oral counterparts, with a rapid onset, minimal to no side-effects and without the risk of adverse events. For patients who are already on oral medications for PDN, topical agents may be used as an adjuvant or may completely replace their oral regimen for pain (Barton et al, 2011; Somberg et al, 2015).

For the purposes of this discussion, it is important to distinguish between topical and transdermal application, as these terms should not be used interchangeably. Topical application aims to achieve a local effect, with very minimal systemic absorption and negligible side-effects. Transdermal application aims to achieve systemic absorption from local application, and the risks of side effects are increased, although possibly less so than if taken orally (Jorge et al, 2010).

Recent literature suggests that peripheral neuropathic pain stems from multiple pathways (Sawynok, 2005). Oral medications typically address only one of these mechanisms, often leading to suboptimal efficacy. Pain is best managed by combination therapy, but combining various oral medications increases risks of adverse events from...
The use of topical analgesics in the management of painful diabetic neuropathy

Drug interactions and side effects, and reduces patient compliance. Combination of various analgesics into a single topical formulation provides multimodal pain control with significantly less risk of the adverse events and drug interactions typically associated with oral therapy. With the exception of local skin reactions – localized allergic reactions or skin irritation – topical pain relief is quite safe. However, it is not the most convenient option when large areas are affected. The advantages of topical analgesics, as compared to oral analgesics are highlighted in Box 2.

**Topical analgesic agents used in the treatment of neuropathic pain**

Multiple therapeutic targets in the skin can be affected by topical analgesia, either alone or in combination with anti-inflammatory agents. Topical therapy, in addition to being safe and effective, typically has a more rapid onset of action and thereby may be considered an important treatment modality for the management of neuropathic pain. *Table 1* summarizes the common doses of agents used in topical preparations.

**Non-steroidal anti-inflammatories (NSAIDs)**

Many clinical trials and reviews have proved the efficacy of topical NSAIDs (notably ibuprofen, diclofenac and ketoprofen) for various musculoskeletal and arthritic pain syndromes (Ahmed et al, 2015; Argoff, 2013). Recently, low-grade inflammation has been identified as a peripheral therapeutic target for PDN and justifies the usage of topical NSAIDs in this condition. NSAIDs work to inhibit the enzyme cyclo-oxygenase, which ultimately blocks the inflammatory cascade. Unlike oral NSAIDs, there have been no renal, cardiac or gastrointestinal adverse events from topical administration, likely due to low systemic absorption (Di Rienzo Businco et al, 2004; Nasri-Heir et al, 2013).

**Lidocaine**

Lidocaine is a targeted peripheral anaesthetic that works by binding to sodium channels on damaged nociceptors and reducing the firing of abnormal action potentials. The use of lidocaine 5% cream, either alone or combined with other topical analgesics, has demonstrated safety and efficacy in the management of painful diabetic neuropathy (Madsen et al, 2013). Recently, a non-inferiority study comparing lidocaine 5% plaster to oral pregabalin (Lyrica) in patients with post-herpetic neuralgia and PDN demonstrated that lidocaine 5% provided similar relief with lower risk of adverse events as compared to pregabalin (Baron et al, 2009).

**Gabapentin**

Gabapentin is an anti-epileptic medication used to treat neuropathic pain. However, its efficacy

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**Box 1. Summary of recommendations for painful diabetic neuropathy (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013).**

1. In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter. In people with type 1 diabetes, annual screening should commence after 5 years’ post pubertal duration of diabetes [Grade D, Consensus].

2. Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10-g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Grade A, Level 1].

3. People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy [Grade A, Level 1A, for type 1 diabetes; Grade B, Level 2, for type 2 diabetes].

4. The following agents may be used alone or in combination for relief of painful peripheral neuropathy:
   a. Anticonvulsants (pregabalin [Grade A, Level 1], gabapentin, valproate [Grade B, Level 2]).
   b. Antidepressants (amitriptyline, duloxetine, venlafaxine) [Grade B, Level 2].
   c. Opioid analgesics (tapentadol extended-release, oxycodone extended-release, tramadol) [Grade B, Level 2].
   d. Topical nitrate spray [Grade B, Level 2].

**Box 2. Advantages of topical analgesics.**

- Increased concentration of drug at site of pain.
- Decreased potential for drug interactions.
- Reduction or elimination of systemic side-effects (eg, sedation, cognitive impairment).
- No adverse effects on internal organs (gastrointestinal, cardiac, renal, or hepatic effect).
- Fast onset of pain relief.
- Localized, targeted relief of pain and inflammation.
- Dose reductions of oral pharmacologic agents.
- Reduced addictive/abuse potential.
- Increased adherence/patient compliance.
- Easy and safe to administer.
The use of topical analgesics in the management of painful diabetic neuropathy

is limited by its dose-related side-effects (Hiom et al, 2015). Although the precise mechanism is unknown, topical administration appears to produce local antinociception.

A recent study by Hiom et al (2015) described the use of topical gabapentin 6% in the treatment of various neuropathic conditions, including painful diabetic polyneuropathy. It was noted that 87% of the patients reported benefit from topical gabapentin, with results achieved within 1 hour of application.

**Tricyclic antidepressants:**

**amitriptyline and doxepin**

Amitriptyline is a tricyclic antidepressant with effective analgesic properties (Saarto and Wiffen, 2007). Side-effects, including dry mouth, constipation, sweating, dizziness, sedation and cardiovascular effects, limit its use (Max et al, 1987; 1992). Its topical use has been widely studied, often in combination with other agents such as topical NSAIDs, lidocaine and ketamine (Gewandter et al, 2014; Barton et al, 2011). Studies reflect dose-related efficacy as well as relief, sometimes within 20 minutes.

Doxepin 5% is commercially available in the US and has been studied and found effective for treatment of PDN. Doses as low as 3% have been shown to be efficacious in the treatment of PDN (McCleane, 2000).

**Clonidine**

Clonidine is an α-2 receptor agonist used to treat hypertension and known to exhibit analgesic properties centrally (Campbell et al, 2012). Topical application of clonidine was found to significantly reduce PDN when 0.1% was applied three times daily, with no significant changes to blood pressure (Byas-Smith et al, 1995).

**Baclofen**

Baclofen is a GABA-b receptor agonist that works as an anti-spasmodic and muscle relaxant centrally and exhibits analgesia peripherally. Research shows promising results when used alone for various neuropathic cases as well as in combination with other topical agents (Fromm et al, 1984). The topical administration of amitriptyline 40mg, baclofen 10mg and ketamine 20mg for patients with chemotherapy-induced neuropathies resulted in improvement of pain and was well tolerated (Barton et al, 2011).

**Ketamine**

Ketamine, a potent analgesic and anaesthetic, works by noncompetitively blocking the excitatory NMDA glutamate receptor. It has been shown to reduce hyperalgesia and allodynia without causing any systemic adverse reactions, and thus is useful in the management of PDN (Hocking and Cousins, 2003).

Concentrations as high as 10% have shown negligible serum levels and its use has been described in a variety of applications for pain management, including post-surgical neuropathic pain, complex regional pain syndrome and post-herpetic neuralgia (Lynch et al, 2003). In another study, a combination of ketamine with amitriptyline and lidocaine significantly reduced pain intensity, sharpness, burning, sensitivity, and itchiness of neuropathic pain due to radiation-induced neuropathy (Uzaraga et al, 2012).

**Nifedipine**

Nifedipine, a calcium channel blocker used orally to treat hypertension, also causes peripheral vasodilation and aids in tissue perfusion. In PDN, it is thought to improve healing and reduce pain by greatly improving tissue perfusion, improving healing and nerve conduction velocity (Goldenberg, 2013).

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**Table 1. Topical analgesics and common strengths.**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Ingredient</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Diclofenac</td>
<td>5–10%</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>5–10%</td>
</tr>
<tr>
<td></td>
<td>Ketoprofen</td>
<td>10–20%</td>
</tr>
<tr>
<td><strong>Anaesthetics</strong></td>
<td>Lidocaine</td>
<td>2–5%</td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>2–10%</td>
</tr>
<tr>
<td><strong>Tri-cyclic antidepressants</strong></td>
<td>Amitriptyline</td>
<td>2–4%</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>3–5%</td>
</tr>
<tr>
<td><strong>Anti-epileptics</strong></td>
<td>Gabapentin</td>
<td>5–10%</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td>Clonidine</td>
<td>0.1–0.2%</td>
</tr>
<tr>
<td><strong>Muscle relaxants</strong></td>
<td>Baclofen</td>
<td>2–5%</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>Nifedipine</td>
<td>2–16%</td>
</tr>
<tr>
<td><strong>Counter-irritant</strong></td>
<td>Capsaicin</td>
<td>0.025–8%</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td>Isosorbide dinitrate</td>
<td>30mg</td>
</tr>
</tbody>
</table>

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Capsaicin
Topical capsaicin, a counter-irritant derived from chili peppers, is a commercially available topical therapeutic agent that is available without a prescription in concentrations of 0.025%, 0.075%, and most recently 8%. However, due to its counter-irritant properties, initial pain upon application considerably limits its use and it has fallen out of favour despite its ready availability. A double-blind, randomized clinical trial compared topical amitriptyline to capsaicin 0.075% in the treatment of PDN and found amitriptyline demonstrated similar efficacy with fewer side-effects (Kiani et al, 2015).

Topical nitrate spray
Isosorbide dinitrate spray is recommended in the treatment of PDN and seems to improve pain and burning sensations by peripheral vasodilation. Patients may experience transient headaches as a side-effect (Agrawal et al, 2007; Yuen et al, 2002).

Conclusion
PDN is a common complication of diabetes that can result in significant limitations to patients’ ability to function and overall quality of life. It is often difficult to treat and can be a source of frustration to both patients and their caregivers. Emerging evidence on the safety and efficacy of topical agents for the relief of neuropathic pain may help to address an unmet need. A growing body of literature has validated both the efficacy and safety of topical treatment for the management of PDN. Topical analgesia is a very promising avenue for clinical improvement in the management of patients with PDN and can be successfully used to supplement or replace conventional systemic analgesic therapy.

“Growing body of literature has validated both the efficacy and safety of topical treatment for the management of PDN.”

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