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Highest in Hierarchy of Evidence: What does Systematic Reviews and Meta-Analyses on Diabetic Peripheral Neuropathy Inform us about Pain?

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Abstract

This short communication was aimed at re-exploring the evidence contribution provided by systematic reviews and meta-analyses on pain in diabetic peripheral neuropathy (DPN) in order to provide implications for anesthetic and analgesic management. Existing evidence though limited provide sufficient information on epidemiology of DPN with prevalence rates ranging between 26-47%;annual pain medication costs of $1,004 per DPN patient;duloxetine, gabapentin, alpha lipoic acid and pregabalin were effective drugs; and consensus guidelines recommended that choice for treatment must also include consideration of adverse effects, individual patient factors such as comorbidities, and often cost.

Keywords: Levels of evidence; Diabetic neuropathy; Neuropathic pain; Evidence-informed pain management; Neuroanesthesiology.

This short communication was aimed a re-exploring the evidence contribution provided by systematic reviews and meta-analyses on pain in diabetic peripheral neuropathy (DPN) in order to provide implications for anesthetic and analgesic management.

Barrett *et al*[1] reviewed the literature examining the epidemiology, quality of life burden, cost, and treatment of diabetic peripheral neuropathy pain (DPNP) through comprehensive computerized literature review of MEDLINE and other databases, which resulted in 321 articles. The prevalence rates ranged between 26-47%., two drugs have been approved by U.S. Food and Drug Administration, DPNP impairs quality of life and one study estimated average annual pain medication costs of $1,004 per DPNP patient.

Many systematic reviews and meta-analyses were on oral pharmacological interventions as he one by Adriaensen *et al*[2] who evaluated the efficacy and safety of oral treatments for DPN in their systematic review of placebo-controlled trials and found that Gabapentin, lamotrigine, tramadol, oxycodone, mexiletine and acetyl-L-carnitine were reported for their efficacy and tolerability.Gabapentin was found to be a first choice treatment in painful diabetic neuropathy, especially in the elderly.

Pluijms *et al*[3] detailed

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the National Institute for Health and Clinical Excellence guidelines for the treatment of painful diabetic neuropathy and opined that "treatment should start with duloxetine or amitriptyline if duloxetine is contraindicated. If pain relief is inadequate, monotherapy with amitriptyline or pregabalin, or combination therapy with amitriptyline and pregabalin should be considered. If pain relief is still insufficient, tramadol instead of or in combination with a second-line agent should be considered. In patients who are unable to take oral medication, topical lidocaine can be considered for localized pain.

Mijnhout *et al*[4] in their systematic review identified studies on effectiveness of alpha lipoic acid by searching MEDLINE and EMBASE and found five RCTs and one meta-analysis which unanimously reported significant improvement in the total symptom score (TSS) when ALA was administered intravenously at a dosage of 600 mg once daily over a period of three weeks.

Four systematic reviews were on Duloxetine: Hall *et al*[5] pooled data from three double-blind, randomized studies on 1139 patients (339 placebo; 800 duloxetine) and 867 patients (287 routine-care; 580 duloxetine) in the acute and extension phases, respectively. Duloxetine was found to be safe and well tolerated, with the three most commonly reported TEAEs being nausea, somnolence and constipation.

Crucitti *et al*[6] evaluated effects of Duloxetine in their meta-analysis and found no short-term improvements in FPG and HbA(1c) compared to placebo, but in the 41-week (n = 181), small and significant long-term improvements was seen in duloxetine-treated patients. Kajdasz *et al*[7] also performed a post hoc analysis to summarize the efficacy and tolerability of duloxetine using number needed to treat (NNT) and number needed to harm (NNH) from three 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies and found that patients receiving duloxetine had NNT of 5 and NNH of 8.8-17.5 which suggested that duloxetine was effective and well tolerated for the management of DPNP.

Duloxetine was compared with pregabalin and gabapentin, and Quilici *et al*[8] conducted an indirect meta-analysis to compare the efficacy and tolerability of duloxetine (DLX), pregabalin (PGB), gabapentin (GBP) and amitriptyline (AMT), using placebo as a common comparator by searching PubMed, EMBASE, CENTRAL Three studies of DLX, six of PGB, two of GBP and none of AMT found all were superior to placebo for all efficacy parameters, with some tolerability trade-offs.

Roth *et al*[9] reviewed nine clinical trials on efficacy and safety of pregabalin in painful diabetic peripheral neuropathy and postherpetic neuralgia by searching MEDLINE and ISI Web of Knowledge and on a total of 2399 patients, Pregabalin (150-600 mg/day) significantly reduced pain and improved pain-related sleep interference.

Sultan *et al*[10] investigated the efficacy of duloxetine in painful diabetic neuropathy and fibromyalgia by searching PubMed, EMBASE (via Ovid), and Cochrane CENTRAL and identified six trials with 1,696 patients: 1,510 were treated with duloxetine and 706 with placebo. The number needed to treat (NNT) for at least 50% pain relief was 6.

Argoff *et al*[11] reviewed the evidence and provided consensus guidelines for treatments and found two agents, duloxetine and pregabalin, were formally approved by the Food and Drug Administration for the treatment of DPNP. The choice for treatment must also include consideration of adverse effects,

individual patient factors such as comorbidities, and often cost.

Existing evidence though limited provide sufficient information on epidemiology of DPN with prevalence rates ranging between 26-47%; annual pain medication costs of $1,004 per DPN patient; duloxetine, gabapentin, alpha lipoic acid and pregabalin were effective drugs; and consensus guidelines recommended that choice for treatment must also include consideration of adverse effects, individual patient factors such as comorbidities, and often cost.

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