Diabetic peripheral neuropathy: pharmacological interventions or acupuncture – an evidence-based perspective

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Abstract
This article demonstrates the practical application of the principles of evidence-based practice (EBP) to derive a solution to a clinical encounter, namely the management of painful peripheral neuropathy. The clinical scenario was analysed in accordance with EBP principles (PICO structure, generation of literature search strategy and citation reference list), concluding with the development of an evidence-based clinical response. Elements of this paper were derived from various assessment components of the author’s in the Evidence Based Practice Unit that is part of Monash University’s graduate studies in wound care programmes.

Evidence-based practice (EBP) principles
The principles of EBP, as first described by Sackett and colleagues provide a clear and concise structure for use in patient care. This straightforward process is a time efficient undertaking, which can effectively ensure patient management, and is supported by the current health literature. EBP may be defined as “a problem-solving approach that incorporates the best available scientific evidence, clinicians’ expertise, and patients’ preferences and values”.

Scenario
A 45 year old, female patient with a 10 year history of poorly controlled type 2 diabetes mellitus presented to an outpatient podiatry clinic complaining of symptoms consistent with painful peripheral neuropathy. Diabetic peripheral neuropathy is a chronic complication of diabetes mellitus defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after other causes have been excluded.” “Painful” diabetic neuropathy reportedly affects approximately 10% of the population and is associated

Table 1. PICO breakdown.

<table>
<thead>
<tr>
<th>Patient, population or problem</th>
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<tbody>
<tr>
<td>Diabetic patients with symptomatic painful peripheral neuropathy. Symptomatic defined as sensory disturbance including pins, needles and tingling</td>
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<table>
<thead>
<tr>
<th>Intervention, prognostic factor, or exposure</th>
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<tr>
<td>Acupuncture</td>
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<table>
<thead>
<tr>
<th>Comparison</th>
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<tbody>
<tr>
<td>Pharmacological agents: anti-convulsants, opioids or tricyclic anti-depressants</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Primary:</td>
</tr>
<tr>
<td>• Pain reduction: Sensory disturbance (measure = reduction in Likert pain score).</td>
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<tr>
<td>• Functional ability: activities of daily living</td>
</tr>
<tr>
<td>Secondary:</td>
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<tr>
<td>• Reduction in adverse effects</td>
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<table>
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<tr>
<th>Type of question</th>
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<tbody>
<tr>
<td>Therapy</td>
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<table>
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<tr>
<th>Type of study</th>
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<tr>
<td>Randomised control trial (RCT): if a large number of RCTs exist in relation to the topic, systematic reviews shall be sought. Alternatively, if insufficient evidence is generated, cohort studies and case control studies shall be utilised</td>
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</table>

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Peripheral neuropathy may be unilateral or bilateral and is typically associated with symptoms of numbness, tingling, sharp pain and burning. A further symptom includes nocturnal exacerbation, linked to sleep deficiency and a reduced quality of life.

Drug therapy commonly utilised in the management of this condition includes anti-convulsants, opioids and tricyclic antidepressants. The question was raised by the patient regarding the comparative benefit of pharmacological agents versus alternative therapy such as acupuncture. A management plan was therefore sought with the objective to reflect EBP through review of the current medical literature in order to provide a definitive, informed clinical response.

**Clinical question**

From the clinical scenario a specific research question was necessary, generated by applying the requirements of a PICO structure. This process requires defining the population (patient group), intervention, and comparison as well as the relevant outcome measures. The aim of this process is to direct a precise and relevant answer to the posed clinical question. Table 1 demonstrates the breakdown from the clinical scenario.

**Literature search**

The next phase was development of a literature search strategy with the objective to provide a response to the clinical question posed, drawing on the PICO elements generated in Table 1 to develop a focused search strategy. The online databases Cochrane Library, Medline, CINAHL, Up To Date and Clinical Evidence were selected to enable comprehensive review of the medical literature. The search strategy outlined below specifically relates to the Ovid Medline Database. Medline was chosen as it is the most comprehensive database for biomedical literature, covering medical and nursing literature. This topic has relevance to medical, nursing and allied health practitioners.

**Search strategy**

When considering effective and efficient literature searching, a comprehensive understanding of the database is required. There is a need to systematically analyse the specific clinical information required by clearly defining parameters such as...
This can be achieved by working through the clinical question in the PICO format.

In addition, prior to commencing a literature search, it is important to generate a clear search strategy. The key to effective and efficient literature searching hinges on the use of appropriate evidence levels, search terms (including MeSH terminology, truncations and Boolean logic) and utilising additional limits such as study type and publication date, in order to achieve the best outcomes.

**PICO**

Generation of the search strategy was based on the concepts of the PICO question:

- **Population group**: symptomatic diabetic peripheral neuropathy.
- **Intervention**: acupuncture.
- **Comparison**: pharmacological agents (anti-convulsants, opioids or tricyclic anti-depressants).
- **Outcomes**: reduction in pain/adverse side effects.

**Evidence levels**

When developing the search strategy, the study designs applicable to the clinical question were considered. The following study designs were ranked according to an evidence hierarchy to include randomised control trials (RCTs), systematic reviews, cohort and case control studies respectively.

**Search terms**

A list of key search terms was generated based on the breakdown of the PICO question. Consideration at this point was given to synonyms, abbreviations and spelling variants. The key terms were: diabetes; diabetic; diabetes mellitus; painful neuropathy; neuropathies; painful peripheral neuropathy; sensory peripheral neuropathy; sensory neuropathy; diabetic neuropathy; acupuncture; alternative therapy; pharmacological management; pharmacological agents; drug therapy; and anti-convulsants, opioids or tricyclic anti-depressants.

The key search list was further refined to include relevant search terminology to ensure greater precision in the search strategy. Search terms were reviewed to include truncation (symbol $=$). For example diabet$ includes the terms diabetes and diabetic. Comparably, neuropath$ captures neuropathy and neuropathies. Other search terminology employed included ‘Adj’ for text words, which must appear next to one another with the text, e.g. painful neuropathy (painful adj. neuropathy). Additionally, ‘tw’ was employed to detect words located within the article title or abstract; this highlights words with a strong theme within the article. The full search list was as follows: Diabet$; Painful adj neuropath$.tw; Diabet$ neuropath$; Alternative therap$; Anti adj convulsants; Tricyclic adj anti adj depressants; and Drug adj therap$.

**Use of medical subject headings (MeSH)**

This function allowed key search terms to be mapped to MeSH vocabulary terminology. MeSH refers to the controlled vocabulary utilised by Medline for indexing of database articles. A number of key subject headings are assigned to articles within the database. Single terms are utilised to represent a particular concept regardless of how these concept have been referred to in the original. For example, the MeSH subject heading diabetic neuropathies was utilised to capture the presence of sensory peripheral neuropathy/sensory neuropathy and diabetic neuropathy. A summary of MeSH subject headings was as follows: Diabetes/; Diabetic Neuropathies/; Acupuncture/; Acupuncture Therapy/; and Complementary Therapy/.

Search research was further refined by limiting results via the FOCUS function and selection of the subcategory [Therapy], to eliminate irrelevant papers.

**Boolean logic**

The concept of Boolean logic allows two or more search terms to be combined using ‘OR’, ‘AND’, ‘NOT’ to increase (OR/AND) or restrict results (NOT). For example, to capture the presence of diabetic and neuropathy, the ‘AND’ function of combined searching was employed.

**Search limitation/expansion**

The following search strategies may be utilised in the literature search to limit and expand the reference list as required. Limitation strategies were as follows:

- Use of Boolean logical ‘AND’ and ‘NOT’, for example peripheral and neuropathy, will ensure both search terms appear in the article.
- Limit to English language only.
- Limit to study type: for example, RCT, systematic review.
- Use of subheading: therapy could be used in this instance as the question relates to a therapy.
- Use of FOCUS: allows selection of subject headings based on the main focus of the article.
- Use of check tags: limit to human studies (www.uic.edu/depts/lib/lhsp/resources/mesh.shtml).

Expansion strategies were as follows:

- Use of ‘OR’ eg. anti-convulsants ‘or’ tricyclic antidepressants.
- Use of ‘No Limits’.
- Use of broad subject terminology.
- Explosion of MeSH category to include more specific terms, allowing multiple subject headings to be searched.
- Truncation of text words.
Citations
Ten citations (Appendix 1) were generated through database search and later sourced to answer the posed clinical question.

Clinical response
A range of pharmacological agents, including anti-convulsants, opioids and tricyclic antidepressants are typically used in the management of painful diabetic neuropathy \(^5, \, 8\). Conversely, acupuncture, considered an alternative therapy, has displayed promise in the medical literature as a treatment strategy \(^6, \, 9\). The following outlines the most recent medical research into the efficacy of these interventions in order to provide a clinical response to the posed scenario.

When considering the comparative benefit of the pharmacological therapies over acupuncture in the management of painful peripheral neuropathy, the current clinical research is lacking. There have been no published studies directly evaluating acupuncture therapies against pharmacological agents. Therefore, the clinical research associated with each class of drug therapy and acupuncture has been evaluated.

Neuropathic pain medications are currently classified according to first line, second-line and other medications; “First-line medications are generally more thoroughly researched and can be used as the sole agent for treatment.” \(^10\). First line medications include Gabapentin (anti-convulsant), controlled-release oxycodone (opioid), and a range of tricyclic antidepressants including amitriptyline, nortriptyline, desipramine, clomipramine and imipramine \(^10\). Due to greater clinical evaluation, first line drug therapies were the focus of the management strategy.

Anti-convulsants
Gabapentin has demonstrated clinical effectiveness in the management of painful diabetic neuropathy \(^10\). This view is confirmed by a RCT conducted by Backonja et al. \(^11\) which illustrated gabapentin mono-therapy (titrated from 900 to 3600mg/d) reduced pain levels associated with diabetic peripheral neuropathy. In terms of secondary outcomes, the study revealed a statistically significant occurrence of dizziness and somnolence in gabapentin-allocated patients versus placebo \(^11\). Other reported side effects included drowsiness, gastrointestinal disturbance, and cognitive impairment documented in elderly patients \(^10\).

Opioids
Opioids are documented to reduce pain levels and improve sleep in diabetic neuropathy \(^10\). Controlled-release oxycodone (maximum level of 120mg/day) provides relief of alldynia (exaggerated response to otherwise non-noxious stimuli) and
Adverse side effects linked to opioid use include constipation, nausea and sedation; additionally falls risk in elderly patients must be considered due to sedation effect.

**Tricyclic antidepressants**

Research involving the tricyclic antidepressants amitriptyline, imipramine and desipramine has shown efficacy in comparison to placebo\(^6\). A study reviewing amitriptyline and desipramine with placebo demonstrated that one of every two patients treated experienced at least moderate relief of neuropathic pain (number needed to treat=2)\(^12\). Outcomes of a Cochrane review of antidepressants for diabetic neuropathic pain supported efficacy of amitriptyline, demonstrating that amitriptyline has an NNT of 1.3 (95% CI 1.2-1.5) to achieve at least moderate pain relief\(^15\). Documented adverse side effects include dry mouth, blurred vision, nausea, vomiting and diarrhoea, associated with malignant arrhythmias in patients with recent myocardial infarction, and may cause tardive dyskinesia\(^8, 12\).

**Acupuncture**

Acupuncture as a management strategy for painful diabetic neuropathy has displayed promising results\(^6, 14, 15\). Acupuncture has demonstrated high levels of success in animal models; yet despite these findings such outcomes have not been replicated in human studies\(^15\). A study by Ahn et al.\(^6\) documented the outcomes of a pilot study which investigated the effect of acupuncture (traditional Chinese medicine versus Japanese acupuncture) in management of painful diabetic neuropathy. The study results reveal lower daily pain severity scores in relation to Japanese acupuncture versus traditional Chinese medicine. However, due to the limited sample size, further studies are required to confirm the validity of such findings.

A study by MacPherson, Thomas, Walters & Fitter\(^16\) investigated the history of side effects of acupuncture in a prospective study of 34,000 acupunctures consultations. Outcomes revealed no serious adverse side effects, defined as requiring hospital admission, prolonged hospital stay, permanent disability or death. Significant minor adverse events were reported at a rate of 1.3 per 1000 treatments, and included severe nausea, fainting, unexpected severe and prolonged aggravation of symptoms, unacceptable pain/brusling, psychological and emotional reactions.

**Comparative studies**

There have been no published studies directly evaluating acupuncture therapies against pharmacological agents. A comparative open label study by Dallocchio, Buffa, Mazzarello & Chirolia\(^17\) reviewed the efficacy of the anti-convulsant gabapentin versus the tricyclic antidepressant amitriptyline. This study illustrated that, whilst both treatments were effective in management of painful diabetic neuropathy, gabapentin demonstrated statistically greater benefit than amitriptyline in measures of pain and paresthesia.

Treatment efficacy of gabapentin and amitriptyline is supported by the RCT outcome of a similar comparative study by Morello \textit{et al.}\(^18\) which reports no statistically significant differences in pain intensity score between the two interventions and similar rates of adverse effects. Caution must be observed in the interpretation of these results due to small sample size of both studies and potential bias of the Dallocchio \textit{et al.}\(^17\) study where non-blinding of study participants was reported.

**Conclusion**

Pharmacological interventions have shown efficacy research studies; however, they frequently fail to provide complete symptomatic relief of painful peripheral neuropathy and are associated with significant side effects\(^19\). Comparatively, acupuncture therapy has shown potential although further research is required.

In light of the current lack of unequivocal comparative research into the management strategies for painful diabetic neuropathy, the clinical evidence supports the clinical benefit of the first line drug therapies, anti-convulsants, opioids, and tricyclic antidepressants, in reducing pain levels. However, it would appear that acupuncture may offer an alternative to individuals who experience adverse side effects associated with use of these pharmacological agents\(^9\). Further studies in this field should reflect rigid study designs to provide definitive comparative data regarding interventions for painful peripheral neuropathy to enhance clinical decision making.

**References**


Appendix 1


Coats S

Diabetic peripheral neuropathy: an evidence-based perspective

Not all mattresses are created equal

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