Pharmacological interventions for painful diabetic neuropathy: Comparative analysis using network meta-analysis

Diabetic peripheral neuropathy is a common complication of diabetes mellitus that disturbs the quality of life of affected persons. Although diabetic neuropathy includes many types of different pathogeneeses and clinical manifestations, the most common type is chronic sensorimotor distal symmetrical polyneuropathy. Among a variety of symptoms as a result of this type of neuropathy, neuropathic pain must be one of the most devastating problems. When painful symptoms are predominant, it is often called ‘painful diabetic neuropathy’ (PDN). It is well known that functionality and quality of life have been deeply disturbed in patients with PDN. Therefore, the therapeutic strategy should be directed toward satisfactory relief of pain symptoms. The first therapeutic step for PDN should be glycemic control. However, patients occasionally require analgesics, even despite glycemic normalization. In addition, the best approach for pain control must be ‘the sooner, the better’ approach. Thus, development of beneficial analgesics are essential. At the present time, several classes of analgesics are available for treating PDN.

There is growing evidence supporting the usefulness of several classes of analgesics for PDN. The most up-to-date guidelines on PDN recommended a few agents as first-line in view of balancing the effectiveness with adverse effects. Overall, the evidence comes from meta-analysis and/or systematic reviews regarding the results of randomized controlled trials (RCTs). Because the design of RCTs has been mostly placebo-controlled, analgesics have seldom been directly compared against each other in terms of effectiveness. Unless direct (head-to-head) comparison is made, the relative merits of the given drugs cannot be definitely determined. Instead, the guidelines based on meta-analysis and systematic reviews determine the order of recommendation by comparing need to treat or odds ratio for achievement 30%, 50% or moderate pain relief taking adverse effects into account among classes of agents or individual agents. Again, in most of the guidelines, the recommendation is not usually based on direct comparison between analgesics. Recently, network meta-analysis (also called multiple treatment comparison meta-analysis) using the Bayesian Markov chain Monte Carlo method (Figure 1) has been introduced to provide estimates of effect sizes for all possible pairwise comparisons regardless of whether or not they have been directly compared in RCTs.

Griebeler et al. carried out a systematic review with the umbrella approach (systematic review of systematic reviews) and network meta-analysis to summarize and evaluate evidence from RCTs, thereby enabling comparison of the relative effectiveness of all included interventions among analgesics. Multiple treatment comparisons simultaneously include both direct and indirect evidence. Indirect and multiple treatment comparisons assume that relevant trials are similar enough in essential features, such as patient characteristics, definitions, and measurements of outcomes and risk of bias in the studies, to be combined. Their network meta-analysis showed that serotonin–norepinephrine reuptake inhibitors, topical capsaicin, tricyclic antidepressants, and anticonvulsants all resulted in larger and significant reduction compared with placebo for short-term (within 3 months) pain control. However, opioids, aldo reductase inhibitors, dextromethorphan, mexiletine and lacosamide did not show a statistically significant difference from placebo. These results rather meet the proposal according to the major guidelines for PDN. In fact, the latter classes of agents have been ranked as second- or third-line in the guidelines. The comparative analysis between classes of agents showed that serotonin–norepinephrine reuptake inhibitors were more effective than anticonvulsants, but not more effective than tricyclic antidepressants (Table 1). In addition, the comparison between individual agents showed that serotonin–norepinephrine reuptake inhibitors, venlafaxine and duloxetine, were significantly superior to pregabalin in pain relief.

Although their report might be the first that evaluates the comparative effectiveness of analgesics for PDN using network meta-analysis, and their new approach might be important and valuable, it should be modest to evaluate them. The authors themselves pointed out that evidence is scant, mostly indirect and often derived from brief trials with an unclear or high risk of bias. Approximately half of the included RCTs had high or unclear risk of bias. The standardized mean difference (SMD) on a pain scale are presented along with the number of direct comparison and percentage of the analyzed RCTs with low risk of bias. Although this description is helpful to evaluate the quality of the presented SMD, it would not be easy to...
Network meta-analysis of analgesics for PDN

First, this class of agents was introduced for the following reasons. First, this class of agents was introduced to target the pathogenesis of diabetic neuropathy (pathogenic treatment). Thus, the cardinal purpose for using these agents is to alleviate nerve lesions, thereby improving sensory symptoms including spontaneous pain. Thus, these agents might not be grouped as analgesics. Most guidelines regarding the treatment for PDN do not include ARIs. Second, the authors stated in the methods of their manuscript that they developed a list of drugs commonly used in the USA and Europe for diabetic neuropathy. However, most of ARIs have failed to appear on the market because of ineffectiveness, adverse effects and so on. In fact, ARIs have not been approved, except for epalrestat in Japan. The development of ARIs other than epalrestat has been discontinued. Third, all RCTs of ARIs have not aimed at alleviation of pain symptoms as the primary end-point for the clinical trials. Thus, more than half of the patients who were enrolled in RCTs did not have painful symptoms, but a variety of sensory symptoms, which included numbness, paresthesia and dysesthesia. In addition, the change of neuropathic symptoms by ARIs have been evaluated differently among RCTs, not standardized.

In their analysis, a variety of anticonvulsants have been analyzed as a class. However, this class of agents might be at least classified into two types – the traditional type, such as carbamazepine and lamotrigine, and the new generation type or calcium channel $\alpha_2\delta$ ligand, such as pregabalin, according to action mechanism, reported effectiveness and adverse effects. Thus, the major guidelines have often evaluated the two types of anticonvulsants separately. This classification might be helpful for the use of such drugs in daily practice. Overall, $\alpha_2\delta$ ligands are believed to be more effective and less common in a mild degree of adverse effects, although there is a sys-

Table 1 | Comparative analgesic effect of serotonin–norepinephrine reuptake inhibitors by class.

| Class and comparator | SMD from direct comparisons (95% CI) | SMD from network meta-analyses (95% CI)† |
|----------------------|-----------------------------------|--------------------------------------|
| Placebo              | $-2.10$ (−3.41 to −0.79)*          | $-1.36$ (−1.77 to −0.95)*             |
| Opioids              | $-0.92$ (−1.72 to −0.09)*          | $-0.69$ (−1.17 to −0.21)*             |
| Aldose reductase inhibitors | $-1.02$ (−2.85 to 0.75) | $-1.06$ (−2.71 to 0.53) |
| Anticonvulsants      | $-0.34$ (−0.63 to −0.05)*          | $-0.45$ (−1.36 to 0.49)              |
| Lacosamide           | $-0.05$ (−1.17 to −0.21)*          | $-0.05$ (−1.16 to 0.01)              |
| Topical capsaicin    | $-0.25$ (−0.78 to 0.28)†           | $-0.58$ (−1.16 to 0.01)              |
| Tricyclic antidepressants | $-0.78$ (0.28)          | $-0.08$ (−2.36 to 0.19)              |
| Dextromethorphan     | $-1.07$ (−1.81 to −0.33)*          | $-1.07$ (−1.81 to −0.33)*            |

CI, confidence interval; SMD, standardized mean difference. *Statistically significant values. †From direct and indirect comparison (refer to ref. 45).
tematic review showing the opposite results, possibly because of the different inclusion criteria and treatment periods⁶. From a practical point of view, such subclassification of anticonvulsants might be appreciated when compared with the magnitude of efficacy and adverse effects among classes.

The authors assessed efficacy at the furthest of multiple time-points separately within 3 months (short-time effect) and longer than 3 months (long-time effect), although the number of long-term RCTs was relatively few. Because most of the RCTs were carried out for 3 months or less, it remains to be clear how long the beneficial effect continues with or without adverse effects, even if the given drugs have been shown to be effective for a 3-month observation period. Longer duration of RCTs needs to be planned for practical management for PDN. This is important, because even if the given drug is considered to be effective, there is no clear evidence of how long we can expect to use it with or without adverse effects in daily practice.

The usefulness of the given drug can be examined from two aspects: efficacy and adverse effects. In the present review, the efficacy was systematically evaluated by SMD on a pain scale. By contrast, adverse effects were descriptively shown, but not statistically processed. Although the method of analysis about adverse effects seems limited, any statistical approach would be appreciated; the odds ratio in terms of withdrawals related to adverse effects or number needed to harm⁶ could be instrumental to daily practice. In view of higher efficacy and lower adverse effects by using smaller doses of each combinator, combination therapy with different mechanisms of action can be rationalized. Although a variety of combined treatments have proved to be effective, any definite or convenient combination has not been established on the basis of clinical use. Further investigation including network meta-analysis would be expected to clarify the potential of any combination.

DISCLOSURE
The author declares no conflict of interest.

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