

Opening new OPTIONS for the treatment of DPNP

Aims: The study aimed to assess the efficacy and tolerability of different combinations of first-line drugs for the treatment of diabetic peripheral neuropathic pain (DPNP).

Methods: OPTION-DM was a multicentre, randomised, double-blind, crossover trial in patients with DPNP with mean daily pain numerical rating scale (NRS) of 4 or higher (scale is 0-10) from 13 UK centres. Participants were randomly assigned (1:1:1:1:1:1), with a predetermined randomisation schedule stratified by site using permuted blocks of size 6 or 12, to receive one of 6 ordered sequences of the 3 treatment pathways: amitriptyline supplemented with pregabalin (A-P), pregabalin supplemented with amitriptyline (P-A), and duloxetine supplemented with pregabalin (D-P), each pathway lasting 16 weeks. The primary outcome was the difference in 7-day average daily pain during the final week of each pathway.

Results: 140 patients were randomly assigned, and 130 started a treatment pathway (with 84 completing at least two pathways) and were analysed for the primary outcome. The 7-day average NRS scores at week 16 decreased from a mean 6.6 (SD 1.5) at baseline to 3.3 (1.8) at week 16 in all 3 pathways. The mean difference was -0.1 (98.3% CI -0.5 to 0.3) for D-P versus A-P, -0.1 (-0.5 to 0.3) for P-A versus A-P, and 0.0 (-0.4 to 0.4) for P-A versus D-P, and thus not significant. Mean NRS reduction in patients on combination therapy was greater than in those who remained on monotherapy (1.0 [SD 1.3] vs. 0.2 [1.5]). Adverse events were predictable for the monotherapies. Increase in dizziness in the P-A pathway, in nausea in the D-P pathway, and in dry mouth in the A-P pathway were observed.

Conclusions: All 3 treatment pathways and monotherapies had similar efficacy. Combination treatment improved pain relief in patients with suboptimal pain control with a monotherapy and was well tolerated.

Comments. Pain is a deeply subjective and personal experience. It is well recognised that DPNP can be very distressing and hard to treat. Most guidelines for DPNP recommend amitriptyline, duloxetine, pregabalin, or gabapentin as initial analgesic treatment for DPNP, but there is little comparative evidence on which one is best or whether they should be combined. The OPTION-DM trial showed that all three treatment pathways reduced the NRS by 3.3 (approx. half the baseline NRS) and were of similar efficacy. Monotherapy resulted in significant pain relief only in just over a third of participants (=who reached NRS <3). It also showed that combination treatment was well tolerated and led to improved pain relief in patients with suboptimal pain control with a monotherapy - an additional 18% of patients reaching NRS <3 and 14% reaching 50% pain relief. One key strength of the OPTION-DM trial was its pragmatic study design, mirroring current neuropathic pain management pathways, where patients are started on monotherapy and escalated to combination therapy, thereby allowing the outcomes of this study to be readily generalisable. The OPTION-DM trial is the largest and longest ever, head-to-head, crossover neuropathic pain trial. The findings are likely to influence DPNP algorithms globally and may even extend to other neuropathic pain syndromes. Importantly, this study was designed and delivered by key, loved, members of Neurodiab - Prof. Solomon Tesfaye and Dr Dinesh Selvarajah, who jointly with the collaborative network of colleagues, both in UK and the EU, many of whom are also Neurodiab members, have delivered a stellar, pivotal moment in DPNP clinical research.

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References. Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, Rajbhandari S, Sharma S, Rayman G, Gouni R, Alam U, Cooper C, Loban A, Sutherland K, Glover R, Waterhouse S, Turton E, Horspool M, Gandhi R, Maguire D, Jude EB, Ahmed SH, Vas P, Hariman C, McDougall C, Devers M, Tsalidis V, Johnson M, Rice ASC, Bouhassira D, Bennett DL, Selvarajah D; OPTION-DM trial group. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. *Lancet*. 2022 Aug 27;400(10353):680-690. doi: 10.1016/S0140-6736(22)01472-6. Epub 2022 Aug 22.

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