Optimal pharmacotherapy pathway in adults with diabetic peripheral neuropathic pain: the OPTION-DM RCT

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Scientific summary

The OPTION-DM RCT

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Scientific summary

Background

There are currently 3.9 million people in the UK with a diagnosis of diabetes, and this is expected to increase to 5.3 million by 2025. Diabetic peripheral neuropathic pain (DPNP) is a serious complication, affecting up to 20–26% of these patients. The mainstay of treatment for DPNP is pharmacotherapy. The National Institute for Health and Care Excellence (NICE) clinical guideline 173 recommends a choice of amitriptyline, duloxetine, pregabalin or gabapentin as initial treatment. However, as NICE points out, the recommendations are not based on robust evidence, as there is a lack of head-to-head randomised controlled trials of current drugs and their combinations.

The OPTION-DM (Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus) trial was designed to examine treatment pathways as a whole, consisting of individual treatments (monotherapy) and their combinations (combination therapy), as this was considered the most applicable to current UK clinical practice.

Objectives

The main aims of the OPTION-DM trial were to determine the most clinically beneficial, cost-effective and tolerated treatment pathway for patients with DPNP. The treatment pathways were amitriptyline supplemented with pregabalin (A-P), duloxetine supplemented with pregabalin (D-P) and pregabalin supplemented with amitriptyline (P-A).

Efficacy objectives

Our primary efficacy objective was to evaluate if at least one of the three pathways is superior to the other pathways in terms of self-reported pain (the primary outcome), tolerability, quality of life (QoL) and cost-effectiveness over a 16-week treatment period. The secondary efficacy objective was to evaluate if at least one monotherapy is superior in improving these outcomes over a 6-week period.

Safety objective

Our safety objective was to describe adverse events (AEs) and serious adverse events (SAEs) between the different treatment pathways.

Subgroup study objective

Our subgroup study objective was to conduct a subgroup study to investigate if patient phenotypes (e.g. demography, type of pain, assessments of mood) predict response to treatment.

Methods

Design

We undertook a randomised crossover trial of treatment pathways to evaluate the superiority of at least one pathway in reducing the 7-day average pain in patients with DPNP.

Setting and participants

Twenty-one secondary care centres in the UK took part (England, $n = 17$; Scotland, $n = 3$; Wales, $n = 1$). Participants were adults with DPNP, with a mean pain score of at least 4 points on an 11-point Numeric Rating Scale (NRS) during the 7-day baseline period, who were willing to wash out their current pain medication and were suitable to receive treatment with the study medications.

Interventions

Participants were randomised with equal allocation (1 : 1 : 1 : 1 : 1 : 1) to one of six treatment sequences, each consisting of three treatment pathways, in random order stratified by treatment centre.

Each treatment pathway was split into two treatment phases. During the first treatment phase, participants received monotherapy with the first-line treatment in the pathway, for 6 weeks.

'Responders' (i.e. patients with a mean 7-day NRS score of ≤ 3 points) continued first-line treatment as a monotherapy for the remainder of the pathway. 'Non-responders' (i.e. patients with a mean 7-day NRS score of > 3 points) commenced combination therapy, with the addition of the second-line treatment in the pathway, for 10 weeks. At the end of a treatment pathway, participants were provided with a taper dose of their current medication for 3 days before commencing wash out of study medication completely for 4 days.

The first and second treatment phases were repeated until the participant had completed all three treatment pathways.

Participants were titrated to a maximum tolerated dose level on starting each new treatment. There were three dose levels for each treatment and the schedule for dose escalation was the same in each pathway. Dose titration decisions were based on treatment response (i.e. 24-hour pain NRS score), side effect profile and participant preference. Participants took medication orally before breakfast and at bedtime.

Participants and the local research team were blinded to treatment allocation, except for the site pharmacist who was unblinded. Blinding was maintained with over-encapsulated capsules and matching placebos. As the study drugs have different dosing schedules (e.g. amitriptyline is given once per day, whereas pregabalin is given twice per day), the placebos were used to ensure that the dosing schedule was identical across the three pathways, with dosing twice per day on all treatments. Participants and sites were aware of whether monotherapy or combination therapy had been prescribed and of the dose level.

Assessment schedule

Participants underwent a 7-day washout prior to randomisation, during which participants were required to stop all existing treatment for neuropathic pain, except paracetamol. Treatments were tapered, usually over a period of 3 days, followed by a 4-day washout period. Participants then entered the baseline period and the pain scores collected during this period were used to determine eligibility. Changes in scores from baseline were calculated in reference to measurements collected during this phase.

Self-reported pain was collected daily by text message and/or patient diary. AEs were recorded at each follow-up visit. After completing all three pathways, participants were asked to choose their preferred treatment. All other assessments were undertaken at 6 and 16 weeks after the start of treatment pathway, which corresponded to the end of monotherapy phase and the end of the treatment pathway, respectively.

Outcome measures

Primary end point

The primary end point was the difference in 7-day average 24-hour pain on an 11-point NRS (0 = no pain and 10 = worst pain imaginable), measured during the final follow-up week of each treatment cycle (i.e. week 16).

Secondary end points

Efficacy

- Seven-day average 24-hour pain (evaluated at patient level) on an 11-point NRS at week 6 among monotherapies.
- The proportion of patients reporting (1) a reduction in pain of 30% from baseline, (2) a reduction in pain of 50% from baseline and (3) a pain score of < 4 points, all at week 16.
- Health-related quality of life and health utility, as assessed by the Short Form questionnaire-36 items and EuroQol-5 Dimensions, five-level version (EQ-5D-5L) inventories at weeks 6 and 16.
- Mood, as assessed by the Hospital Anxiety and Depression Scale at weeks 6 and 16.
- Pain interference with function, measured by the Brief Pain Inventory – Modified Short Form at weeks 6 and 16.
- Insomnia, measured by the Insomnia Severity Index at weeks 6 and 16.
- Patient Global Impression of Change at week 16.
- Participant's preferred treatment, reported on completion of all three pathways at week 50.

Cost-effectiveness

- The cost–utility analysis compared the incremental quality-adjusted life-years (QALYs) (derived from the EQ-5D-5L) and costs for the three treatment pathways from the perspective of the NHS and social care.

Safety

- Adverse events were summarised as the number of patients experiencing each type of event, the number of events and the intensity, seriousness, relationship and duration of event.

Subgroups and exploratory analyses

- Subgroup analyses were undertaken for pain in relation to (1) age, (2) pain score at baseline, (3) pain phenotype (derived from the Neuropathic Pain Symptom Inventory), (4) anxiety and depression scores at baseline, (5) previous medication and (6) the COVID-19 lockdown restrictions. Additional analyses were performed to compare outcomes among patients on combination therapy with patients who remained on monotherapy.

Patient's perceived tolerability

- Difference in tolerability among pathways, evaluated at the patient level on an 11-point NRS at weeks 6 and 16.

Sample size and analysis

The study sought to detect a mean difference of 0.5 points in 7-day NRS between any two pathways. This was consistent with the effect size previously reported in the active comparison of a previous crossover study and equates to an approximate 8% difference in the proportion of people improving by at least 1 point, that is, a minimally clinically significant reduction in an individual. Assuming a within-patient standard deviation (SD) of 1.65, an alpha of 0.0167 to allow for three pairwise comparisons, a 25% drop-out rate and 90% power, the study sought to randomise 392 participants.

However, recruitment for this demanding trial, with multiple study visits and four washout periods, became challenging and difficult to justify, given that most previous similar trials had used a 1-point difference on the NRS. With approval from the Trial Steering Committee, our patient and public involvement panel and the funder, a decision was made to continue recruitment to a fixed time

(July 2019), at which point the trial had recruited 140 participants. Using our original assumptions (i.e. a within-patient SD of 1.65 and an alpha of 0.0167), this provided over 90% power to detect a difference of 1 NRS point and was sufficient to estimate differences in average pain to within a standard error of 0.25 NRS points.

Analyses were undertaken using generalised mixed-effect modelling, with treatment group (i.e. A-P, D-P or P-A) and pathway order (i.e. first, second or third) as fixed-effect covariates and participant as a random intercept. Subgroup analyses were undertaken by adding an interaction term to the model and reported as marginal means. The impact of missing data was assessed for the primary outcome using last observation carried forward, multiple imputation and controlled multiple imputation (the latter imputed more pessimistic pain scores for participants who withdrew treatment due to toxicity, intolerability or inadequate pain relief).

Statistical comparisons used 98.3% confidence intervals (CIs) and a 0.0167 statistical significance level, whereas economic analyses used 95% CIs and a 5% significance level. Additional post hoc analyses were undertaken to assess whether outcomes were temporally associated with the COVID-19 lockdown, which began 3 months before the last patient last visit.

Results

Between November 2017 and July 2019, a total of 140 participants were randomised from 13 trial centres across the UK, of whom 130 were included in the analyses. Self-rated pain at 16 weeks was similar between the arms during the pathway. A total of 130 patients with average pain score of 6.6 out of 10 were analysed, of whom 84 started all three pathways. The 7-day average pain score reduced from a mean of 6.6 (SD 1.5) points at baseline to 3.3 (SD 1.8) points at week 16 in all three groups. The mean difference for D-P compared with A-P was −0.1 (98.3% CI −0.5 to 0.3) points, for P-A compared with A-P was −0.1 (98.3% CI −0.5 to 0.3) points and for P-A compared with D-P was 0.0 (98.3% CI −0.4 to 0.4) points. These findings were robust across a range of analyses assessing missing data under plausible scenario. Pain continued to drop following the introduction of combination therapy from week 6 onward, suggesting that combination therapy may offer additional benefit beyond monotherapy alone. Tolerability, discontinuation and QoL were also similar, but patients experienced greater levels of insomnia on D-P than A-P, and the safety profiles differed with regard to dizziness (highest in the P-A arm), nausea (highest in the D-P arm) and dry mouth (highest in the A-P arm). The P-A pathway had the smallest number of patients discontinuing first-line monotherapy because of treatment-emergent AEs and was, therefore, numerically the preferred pathway of the patients (most commonly preferred by participants: A-P, 24%; D-P, 33%; P-A, 43%; $p = 0.26$).

The incremental QALY gain was small for each pathway comparison [A-P vs. D-P −0.002 (95% CI −0.011 to 0.007), A-P vs. P-A −0.006 (95% CI −0.002 to 0.014) and D-P vs. P-A 0.007 (95% CI 0.0002 to 0.015)] and incremental costs over 16 weeks were also similar [A-P vs. D-P −£113 (95% CI −£381 to £90) A-P vs. P-A £155 (95% CI −£37 to £625) and D-P vs. P-A £141 (95% CI −£13 to £398)]. No one pathway dominated the others in cost-effectiveness analysis. Results remained uncertain in sensitivity analysis that used an alternative algorithm for utility values for the EQ-5D-5L and also incorporated costs borne by the patients and their carers.

Conclusions

The three treatment pathways and monotherapies showed comparable reduction in pain. The P-A pathway led to less monotherapy discontinuation due to treatment-emergent AEs and may be preferred. Maximum tolerated combination treatment was well tolerated and resulted in better pain relief than maximum tolerated monotherapy. The findings of this head-to head trial will inform future NICE guidance that currently does not recommend combination treatment.

Trial registration

The trial is registered as ISRCTN17545443 and EudraCT 2016-003146-89.

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