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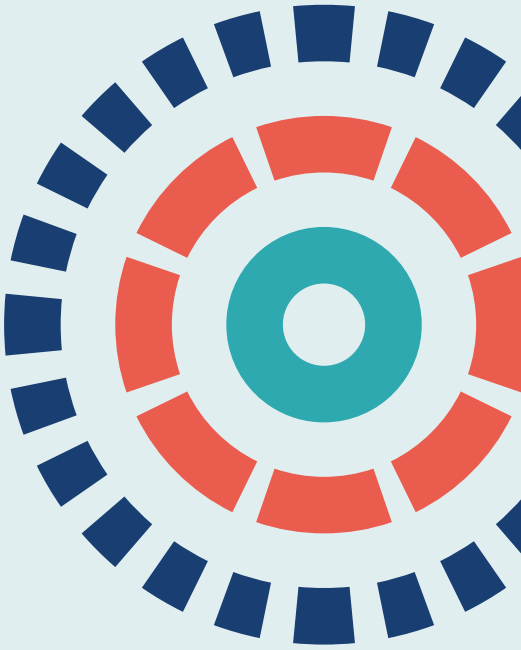

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Optimal pharmacotherapy pathway in adults with diabetic peripheral neuropathic pain: the OPTION-DM RCT

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Abstract

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

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Background: The mainstay of treatment for diabetic peripheral neuropathic pain is pharmacotherapy, but the current National Institute for Health and Care Excellence guideline is not based on robust evidence, as the treatments and their combinations have not been directly compared.

Objectives: To determine the most clinically beneficial, cost-effective and tolerated treatment pathway for diabetic peripheral neuropathic pain.

Design: A randomised crossover trial with health economic analysis.

Setting: Twenty-one secondary care centres in the UK.

Participants: Adults with diabetic peripheral neuropathic pain with a 7-day average self-rated pain score of ≥ 4 points (Numeric Rating Scale 0–10).

Interventions: Participants were randomised to three commonly used treatment pathways: (1) amitriptyline supplemented with pregabalin, (2) duloxetine supplemented with pregabalin and (3) pregabalin supplemented with amitriptyline. Participants and research teams were blinded to treatment allocation, using over-encapsulated capsules and matching placebos. Site pharmacists were unblinded.

Outcomes: The primary outcome was the difference in 7-day average 24-hour Numeric Rating Scale score between pathways, measured during the final week of each pathway. Secondary end points included 7-day average daily Numeric Rating Scale pain score at week 6 between monotherapies, quality of life (Short Form questionnaire-36 items), Hospital Anxiety and Depression Scale score, the proportion of patients achieving 30% and 50% pain reduction, Brief Pain Inventory – Modified Short Form items scores, Insomnia Severity Index score, Neuropathic Pain Symptom Inventory score, tolerability (scale 0–10), Patient Global Impression of Change score at week 16 and patients' preferred treatment pathway at week 50. Adverse events and serious adverse events were recorded. A within-trial cost–utility analysis was carried out to compare treatment pathways using incremental costs per quality-adjusted life-years from an NHS and social care perspective.

Results: A total of 140 participants were randomised from 13 UK centres, 130 of whom were included in the analyses. Pain score at week 16 was similar between the arms, with a mean difference of −0.1 points (98.3% confidence interval −0.5 to 0.3 points) for duloxetine supplemented with pregabalin compared with amitriptyline supplemented with pregabalin, a mean difference of −0.1 points (98.3% confidence interval −0.5 to 0.3 points) for pregabalin supplemented with amitriptyline compared with amitriptyline supplemented with pregabalin and a mean difference of 0.0 points (98.3% confidence interval −0.4 to 0.4 points) for pregabalin supplemented with amitriptyline compared with duloxetine supplemented with pregabalin. Results for tolerability, discontinuation and quality of life were similar. The adverse events were predictable for each drug. Combination therapy (weeks 6–16) was associated with a further reduction in Numeric Rating Scale pain score (mean 1.0 points, 98.3% confidence interval 0.6 to 1.3 points) compared with those who remained on monotherapy (mean 0.2 points, 98.3% confidence interval −0.1 to 0.5 points). The pregabalin supplemented with amitriptyline pathway had the fewest monotherapy discontinuations due to treatment-emergent adverse events and was most commonly preferred (most commonly preferred by participants: amitriptyline supplemented with pregabalin, 24%; duloxetine supplemented with pregabalin, 33%; pregabalin supplemented with amitriptyline, 43%; $p = 0.26$). No single pathway was superior in cost-effectiveness. The incremental gains in quality-adjusted life-years were small for each pathway comparison [amitriptyline supplemented with pregabalin compared with duloxetine supplemented with pregabalin −0.002 (95% confidence interval −0.011 to 0.007) quality-adjusted life-years, amitriptyline supplemented with pregabalin compared with pregabalin supplemented with amitriptyline −0.006 (95% confidence interval −0.002 to 0.014) quality-adjusted life-years and duloxetine supplemented with pregabalin compared with pregabalin supplemented with amitriptyline 0.007 (95% confidence interval 0.0002 to 0.015) quality-adjusted life-years] and incremental costs over 16 weeks were similar [amitriptyline supplemented with pregabalin compared with duloxetine supplemented with pregabalin −£113 (95% confidence interval −£381 to £90),

amitriptyline supplemented with pregabalin compared with pregabalin supplemented with amitriptyline £155 (95% confidence interval −£37 to £625) and duloxetine supplemented with pregabalin compared with pregabalin supplemented with amitriptyline £141 (95% confidence interval −£13 to £398)].

Limitations: Although there was no placebo arm, there is strong evidence for the use of each study medication from randomised placebo-controlled trials. The addition of a placebo arm would have increased the duration of this already long and demanding trial and it was not felt to be ethically justifiable.

Future work: Future research should explore (1) variations in diabetic peripheral neuropathic pain management at the practice level, (2) how OPTION-DM (Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus) trial findings can be best implemented, (3) why some patients respond to a particular drug and others do not and (4) what options there are for further treatments for those patients on combination treatment with inadequate pain relief.

Conclusions: The three treatment pathways appear to give comparable patient outcomes at similar costs, suggesting that the optimal treatment may depend on patients' preference in terms of side effects.

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

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
A-P	amitriptyline supplemented with pregabalin
AST	aspartate aminotransferase
BNF	*British National Formulary*
BPI-MSF	Brief Pain Inventory – Modified Short Form
CI	confidence interval
CRF	case report form
CSRI	Client Service Receipt Inventory
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DN4	Douleur Neuropathique 4
D-P	duloxetine supplemented with pregabalin
DPNP	diabetic peripheral neuropathic pain
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	glycated haemoglobin
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IMP	investigational medicinal product
ISI	Insomnia Severity Index
mTCNS	modified Toronto Clinical Neuropathy Score
NICE	National Institute for Health and Care Excellence
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numeric Rating Scale
OPTION-DM	Optimal Pathway for TreatIng neurOpathic paiN in Diabetes Mellitus
P-A	pregabalin supplemented with amitriptyline
PGIC	Patient Global Impression of Change
PI	principal investigator
PPI	patient and public involvement
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SCRAM	Sheffield Clinical Trials Research Unit online randomisation system
SD	standard deviation
SF-36	Short Form questionnaire-36 items
SMS	short message service
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

Plain English summary

The number of people with diabetes is growing rapidly in the UK and is predicted to rise to over 5 million by 2025. Diabetes causes nerve damage that can lead to severe painful symptoms in the feet, legs and hands. One-quarter of all people with diabetes experience these symptoms, known as 'painful diabetic neuropathy'. Current individual medications provide only partial benefit, and in only around half of patients. The individual drugs, and their combinations, have not been compared directly against each other to see which is best.

We conducted a study to see which treatment pathway would be best for patients with painful diabetic neuropathy. The study included three treatment pathways using combinations of amitriptyline, duloxetine and pregabalin. Patients received all three treatment pathways (i.e. amitriptyline treatment for 6 weeks and pregabalin added if needed for a further 10 weeks, duloxetine treatment for 6 weeks and pregabalin added if needed for a further 10 weeks and pregabalin treatment for 6 weeks and amitriptyline added if needed for a further 10 weeks); however, the order of the treatment pathways was decided at random. We compared the level of pain that participants experienced in each treatment pathway to see which worked best.

On average, people said that their pain was similar after each of the three treatments and their combinations. However, two treatments in combination helped some patients with additional pain relief if they only partially responded to one. People also reported improved quality of life and sleep with the treatments, but these were similar for all the treatments. In the health economic analysis, the value for money and quality of life were similar for each pathway, and this resulted in uncertainty in the cost-effectiveness conclusions, with no one pathway being more cost-effective than the others. The treatments had different side effects, however; pregabalin appeared to make more people feel dizzy, duloxetine made more people nauseous and amitriptyline resulted in more people having a dry mouth. The pregabalin supplemented by amitriptyline pathway had the smallest number of treatment discontinuations due to side effects and may be the safest for patients.

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.

Funding

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Chapter 1 Introduction

Scientific background

There are currently 3.9 million people in the UK with a diagnosis of diabetes and, if the numbers continue to increase at the current rate, it is expected that this will increase to 5.3 million people by 2025.[4] Diabetic peripheral neuropathic pain (DPNP) is a serious complication affecting up to 20–26% of these patients.[5,6] With the prevalence of diabetes set to increase by epidemic proportions over the next decade, DPNP will pose a major treatment challenge.[7,8]

Diabetic peripheral neuropathic pain causes burning, deep aching and 'electric shock'-like lancinating (also described as 'stabbing or knife-like') pains; contact pain, often with day-time clothes and bedclothes (allodynia); pain on walking, often described as 'walking barefoot on marbles' or 'walking barefoot on hot sand'; sensations of heat or cold in the feet; a persistent achy feeling in the feet and cramp-like sensations in the legs.[8] With advanced disease, the pain can extend above the feet and may involve the whole of the legs. When this is the case, then there is often upper limb involvement also. Moderate to severe unremitting lower limb pain is present in over 70% of sufferers[6,9] and can cause insomnia, poor quality of life (QoL), unemployment and depression.[10–13]

The mainstay of treatment for DPNP is pharmacotherapy. The National Institute for Health and Care Excellence (NICE) clinical guideline 173[14] recommends a choice of amitriptyline, duloxetine, pregabalin or gabapentin as initial treatment. All are licensed treatments for DPNP, except amitriptyline, which has been used off-licence for more than 25 years. There is moderate evidence for the efficacy of each drug based on Cochrane reviews[15–18] and meta-analyses,[19–21] but the best we can hope for with any monotherapy is 50% pain relief in 50% of patients.[14] This is often accompanied by side effects (dry mouth, constipation, sedation, dizziness, falls, nausea, oedema, etc.) in around 10–20% of patients, depending on dose. NICE recommends combination treatment if initial treatment is not effective (the majority).[14] However, as NICE points out, recommendations are not based on robust evidence because (1) there are few well-designed head-to-head studies comparing the first-line drugs and their combinations, (2) most studies were flawed with inadequate power, inappropriate end points or short duration of follow-up, and (3) many randomised controlled trials (RCTs) lacked appropriate health-related quality of life (HRQoL) measures, including functionality, and failed to measure the impact of drug-related adverse effects on health economics and QoL.[14] A RCT is, therefore, needed to address these deficiencies.

Rationale for research

Recent Cochrane reviews,[15–18] meta-analyses,[19–21] consensus guidelines[22–24] and NICE clinical guidance 173[14] support the choice of amitriptyline (25–75 mg/day), duloxetine (60–120 mg/day) and the $\alpha 2\delta$ agonists pregabalin (300–600 mg/day) and gabapentin (0.9–3.6 g/day) as first-line agents for DPNP. However, these recommendations are not based on solid evidence.

Comparator studies

Two small randomised double-blind crossover short-duration (5 weeks' follow-up) studies compared amitriptyline with pregabalin ($n = 51$)[25] and amitriptyline with duloxetine ($n = 58$)[26] in DPNP. The studies were underpowered to detect any differences in pain relief between the drugs. Another underpowered, and short (4 weeks), RCT compared amitriptyline ($n = 27$), duloxetine ($n = 28$) and pregabalin ($n = 28$),[27] and found no differences between the groups. The lack of head-to-head studies led to an indirect comparison of the efficacy and tolerability of duloxetine with pregabalin, using placebo as a common comparator, but this comparison found no difference in 24-hour pain severity between the two.[28]

Combination studies

Low-dose combination therapy with gabapentin and morphine was more effective than higher doses of either,[29] although, curiously, there was no difference between placebo and gabapentin.[30] Finally, the COMBO-DN (COmbination vs Monotherapy of pregaBalin and dulOxetine in Diabetic Neuropathy) study,[31] which, to the best of our knowledge, is the largest combination study in DPNP ($n = 804$), assessed whether or not combining standard doses of duloxetine (60 mg/day) and pregabalin (300 mg/day) was superior to maximum doses of either. The COMBO-DN study[31] also compared head to head the standard doses of duloxetine and pregabalin and found no difference in the change in 24-hour average pain or number of adverse events (AEs) between standard-dose combination therapy and high-dose monotherapy.[31] Although the standard dose of duloxetine was superior to pregabalin, there was equivalent efficacy with pregabalin at higher doses.[31]

Published economic evaluations

To date, no trial has provided conclusive evidence regarding the cost-effectiveness of amitriptyline, duloxetine and pregabalin for DPNP. Wu *et al.*[32] conducted a cost–utility analysis of duloxetine compared with usual care as part of an open-label study extension and concluded that duloxetine was a dominant treatment (i.e. more effective and less costly). However, methodological issues limit the generalisability of this conclusion. Beard *et al.*[33] developed a short-term decision tree to estimate alternative treatment sequences that include duloxetine. A standard treatment sequence was defined as amitriptyline, gabapentin and then opioid-related treatment. Duloxetine was evaluated as a first-, second-, third- or fourth-line therapy. First-line use of duloxetine was both the most effective and most cost-effective treatment strategy. O'Connor *et al.*[34] compared the costs and quality-adjusted life-years (QALYs) of first-line desipramine, duloxetine, gabapentin and pregabalin, and concluded that desipramine and duloxetine may be more cost-effective than gabapentin or pregabalin for first-line treatment of DPNP. In 2012, de Salas Cansado *et al.*[35] conducted an economic evaluation of pregabalin compared with usual care in the management of community-treated patients with refractory painful diabetic peripheral neuropathy in Spain. de Salas Cansado *et al.*[35] compared costs and QALYs from a Spanish NHS and societal perspective and concluded that pregabalin may be cost-effective. The limited published evidence highlights the need for a definitive evaluation of the costs and health benefits of alternative treatment sequences for DPNP. This evidence would inform NHS guidance and commissioning and ensure an efficient use of limited health resources.

In summary, there is a lack of head-to-head studies of current drugs and their combinations, highlighting the need for carefully designed RCTs, involving patients recruited from both primary and secondary care, to identify the most cost-effective and best-tolerated treatment pathway for DPNP.

Intervention

The OPTION-DM trial was a randomised crossover trial of treatment pathways to evaluate the superiority of at least one pathway [i.e. amitriptyline supplemented with pregabalin (A-P), duloxetine supplemented with pregabalin (D-P) and pregabalin supplemented with amitriptyline (P-A)] in reducing the 7-day average 24-hour pain in patients with DPNP.

Each treatment pathway consisted of two periods (i.e. 6 weeks' monotherapy followed by 10 weeks' combination therapy).

Why exclude gabapentin?

The rationale for not studying two $\alpha 2\delta$ agonists (i.e. pregabalin and gabapentin) is that:

- The evidence for gabapentin is derived from only one reasonable-quality RCT with a 4-week titration and a 4-week treatment phase[36] (vs. seven RCTs for pregabalin and evidence supported by meta-analysis[19]).
- Gabapentin is a thrice-daily drug.
- In contrast to pregabalin, the pharmacokinetics of gabapentin are not linear, and a long titration period of up to 2 months[23] is necessary to avoid toxicity.

Why examine treatment pathways?

Although a head-to-head RCT of individual drugs and a separate RCT of combination therapy could be designed, in our opinion an examination of a treatment pathway as a whole is the most efficient and applicable to current UK clinical practice. This is because most patients are started on monotherapy and will require a second agent added in combination within a few months. Only a minority of patients will either have massive benefit from monotherapy [i.e. 24-hour pain scores of < 3 points on a Numeric Rating Scale (NRS)] and will not need another agent or will not tolerate monotherapy (or monotherapy will be completely ineffective) and will be switched to another agent. Therefore, the OPTION-DM trial, which examined the whole treatment pathway, captured more clinically relevant outcomes than artificially designed head-to-head monotherapy or combination studies. Hence, the outcomes of this study will be readily generalisable to current UK clinical practice.

Which treatment pathways?

The three treatment pathways studied in the OPTION-DM trial were (1) A-P, (2) P-A and (3) D-P.

We did not examine the pathway of pregabalin supplemented by duloxetine because of the COMBO-DN study findings.[31] In the COMBO-DN study, there was no difference in pain reduction if pregabalin was added to duloxetine, or vice versa.[31] However, duloxetine was superior to pregabalin as an initial treatment, is a once daily preparation and is also the cheaper option in the UK. There is, therefore, a good rationale for starting patients on duloxetine and then adding pregabalin in combination. Finally, as both amitriptyline and duloxetine are antidepressants, there was little rationale for combining both.

Efficient design with 16-week treatment pathways

This was an efficiently designed head-to-head crossover RCT,[37] with each patient undergoing all pathways. The duration of monotherapy in each pathway was at least 6 weeks, which is an adequate duration to assess treatment effect and whether or not combination therapy is indicated.[23,37] The subsequent 10-week combination therapy in patients with partial benefit from monotherapy is adequate to assess stabilised treatment outcomes.[31]

Objectives

The main aims of this study were to determine the most clinically beneficial, cost-effective and tolerated treatment pathway for patients with DPNP.

Efficacy objectives

The efficacy objectives were to evaluate if at least one of the three pathways is superior to the other pathways in improving self-reported pain, as measured by a NRS (the primary outcome), tolerability, QoL and cost-effectiveness over a 16-week treatment period. The secondary efficacy objective was to evaluate if at least one monotherapy is superior to a different monotherapy in improving the same outcomes.

Safety objective

The safety objective was to describe AEs and serious adverse events (SAEs) data (summarised both at patient level and event level) between the different treatment pathways.

Subgroup study objectives

We conducted a subgroup study to investigate if patient phenotypes (demography, type of pain, assessments of mood, sleep, etc.) predict response to treatment.

Chapter 2 Methods

Sections of this chapter have been reproduced from the published OPTION-DM trial protocol.[2] The text below includes minor additions and formatting changes to the original text.[3]

Study design

This was a randomised crossover trial of treatment pathways to evaluate the superiority of at least one pathway (i.e. A-P, D-P and P-A) in reducing the 7-day average 24-hour pain in patients with DPNP. Eligible patients were randomised to one of six treatment sequences, with equal allocation to sequences (1 : 1 : 1 : 1 : 1 : 1). Each sequence examined all three treatment pathways in random order. Each treatment pathway consisted of two phases (i.e. 6 weeks' monotherapy followed by 10 weeks' monotherapy or 10 weeks' combination therapy based on response to treatment).

Figure 1 shows a schematic representation of the study schedule. Following the screening, consent and initial washout visits (i.e. weeks −2 to 0), the visits from week 0 to week 16 were repeated until all three treatment pathways were completed. Face-to-face assessments were completed at the week numbers indicated in *Figure 1*. Weekly telephone calls were carried out between study visits.

Trial approvals and registration

The trial was approved by the Yorkshire and the Humber – Sheffield Research Ethics Committee (reference 16/YH/0459) on 9 December 2016. The Medicines and Healthcare products Regulatory Agency issued the clinical trial authorisation on 23 June 2017 (reference 21304/0262/001-0001, EudraCT reference 2016-003146-89).

The trial was registered as ISRCTN17545443.

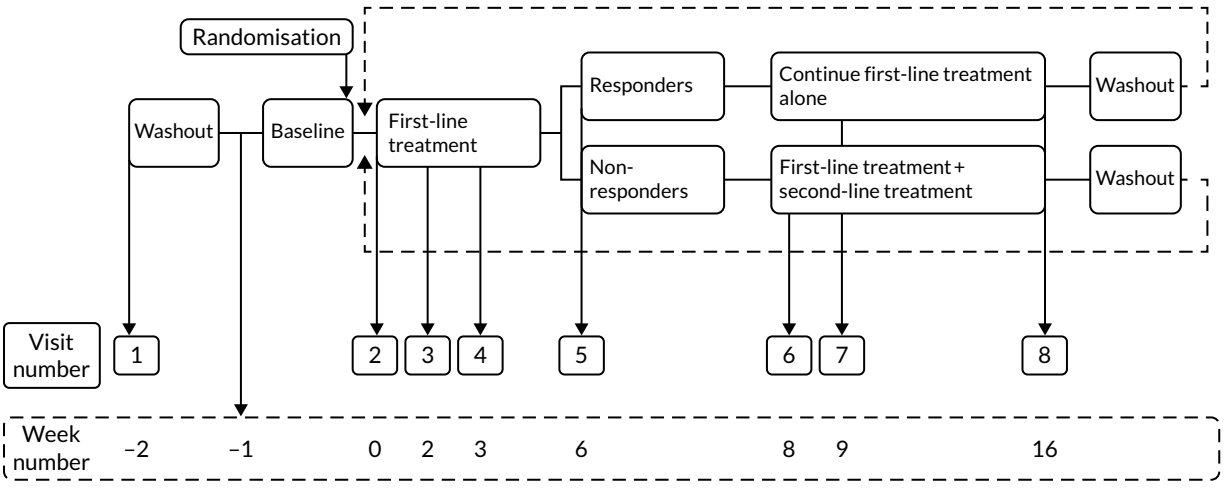

FIGURE 1 Study schedule.

Participant eligibility criteria

Inclusion criteria

Participants were required to meet all of the following inclusion criteria:

- Age ≥ 18 years.
- Neuropathic pain affecting feet and/or hands for at least 3 months or taking pain medication for neuropathic pain for at least 3 months.
- Bilateral distal symmetrical neuropathic pain confirmed by the Douleur Neuropathique 4 (DN4)[38] questionnaire at screening visit. The participant was eligible if four or more questions were answered as 'yes'.
- Bilateral distal symmetrical polyneuropathy confirmed by a modified Toronto Clinical Neuropathy Score (mTCNS)[39] of > 5 points at screening visit.
- Stable glycaemic control [i.e. glycated haemoglobin (HbA_{1c}) < 108 mmol/mol].
- A mean total pain intensity of at least 4 points on an 11-point NRS (with 0 being 'no pain' and 10 'worst pain imaginable') during 1 week off pain medications (i.e. the baseline period). Patients could be invited to attend the randomisation visit sooner if it was clear that their mean pain score for the week was ≥ 4, that is, as soon as the total sum of the pain scores was ≥ 28 points (e.g. randomisation could take place after 3 days if a patient scored 10 on each of the first 3 days of monitoring). This was to minimise the length of time patients remained off neuropathic pain treatments.
- Patient is willing and able to comply with all the study requirements and be available for the duration of the study.
- Patient is willing to discontinue current neuropathic pain-relieving medications.
- Informed consent form for study participation signed by participant.

Exclusion criteria

Patients were not eligible for the study if they met any of the following exclusion criteria:

- Non-diabetic symmetrical polyneuropathies.
- History of alcohol/substance abuse that would, in the opinion of the investigator, impair the patient's ability to take part in the study.
- History of severe psychiatric illnesses that would, in the opinion of the investigator, impair the patient's ability to take part in the study.
- History of epilepsy.
- Contraindications to study medications.
- Pregnancy/breastfeeding or planning pregnancy during the course of the study.
- Use of prohibited concomitant treatment that could not be discontinued with the exception of prior concomitant and safe use of selective serotonin reuptake inhibitors (SSRIs) with study medication (duloxetine and/or amitriptyline). Note that concomitant use of citalopram was not permitted.
- Use of a high-dose morphine equivalent (> 100 mg/day).
- Liver disease [i.e. aspartate aminotransferase (AST)/alanine aminotransferase (ALT) two or more times the upper limit of normal].
- Significant renal impairment [i.e. an estimated glomerular filtration rate (eGFR) of < 30 ml/minute/1.73 m^2].
- Heart failure (i.e. New York Heart Association ≥ class III).
- Clinically significant cardiac arrhythmias on 12-lead electrocardiogram, current history of arrhythmia, second- or third-degree heart block or left bundle branch block (patients with right bundle branch block or first-degree heart block may be included following discussion with cardiology team).
- Patients with a recent myocardial infarction (< 6 months prior to randomisation).
- Symptomatic postural hypotension that, in the opinion of the investigator, is clinically significant and would be a contraindication to the study medication.

- Prostatic hypertrophy or urinary retention to an extent that would, in the opinion of the investigators, be a contraindication to the study medication.
- Patients with other painful medical conditions where the intensity of the pain is significantly more severe than their DPNP (patients were not excluded if the pain was transient in nature).
- Any suicide risk, as judged by the investigator or as defined by a score of ≥ 2 points on the Suicide Risk Questionnaire.
- Significant language barriers that are likely to affect the participant's understanding of the medication schedule or ability to complete outcome questionnaires.
- Concurrent participation in another clinical trial of an investigational medicinal product (IMP).
- Major amputations of the lower limbs.
- Foot ulcers, only if, in the opinion of the local principal investigator (PI), they were likely to have a confounding/detrimental effect on study primary outcome or participation (e.g. localised foot pain from the ulcer site).

Withdrawals

Participants could choose to withdraw from the trial treatment or follow-up at any time. The local research team could also choose to discontinue the study treatment for clinical reasons or if the participant's condition changed following randomisation so that they met one or more of the exclusion criteria. Outcome data were collected up to the end of the current treatment pathway, if possible. Data already collected up to the point of withdrawal were kept.

Settings and locations where the data were collected

Initially, the trial planned to recruit participants from eight secondary care hospital sites across the UK. Additional sites were added during the trial, and a total of 21 sites were opened to recruitment during the course of the trial.

Potential participants were identified directly through the database and via clinics at participating centres, as well as via participant identification centres, podiatry clinics and general practice mail-outs. Recruitment strategies differed between sites to reflect the local organisational structure at each site.

Participant treatment and outcome data collection was carried out by the recruiting hospital site. All research activity at the site was carried out by hospital employees trained in OPTION-DM trial processes.

Screening, assessment of eligibility and consent

Prior to any study procedures being completed, participants were required to give written informed consent for the study. The participant was given sufficient time to ask questions, consider the study and discuss it with family/friends prior to providing consent, which was taken by medically qualified site investigators.

Eligibility for the study was assessed by the local investigator. Participants were required to stop all existing treatment for neuropathic pain, except paracetamol, if applicable. 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.

Randomisation

Randomisation was completed using the Sheffield Clinical Trials Research Unit (CTRU) online randomisation system (SCRAM). Participants were assigned to one of six sequences (allocation 1 : 1 : 1 : 1 : 1 : 1) based on a

predetermined randomisation schedule and stratified by site using permuted blocks of sizes 6 or 12. The trial statistician created the randomisation schedule. Each sequence consisted of three treatment pathways given in random order. The three treatment pathways were:

1. A-P (i.e. first-line amitriptyline, second-line pregabalin)
2. D-P (i.e. first-line duloxetine, second-line pregabalin)
3. P-A (i.e. first-line pregabalin, second-line amitriptyline).

Members of the research teams at participating sites were granted access to the SCRAM system with individual usernames and passwords. These members of staff were responsible for performing the randomisation process once eligibility had been confirmed by the local investigator. After the randomisation was completed, the pharmacy department was informed that a new participant had been randomised. A member of the pharmacy team then accessed the SCRAM system to obtain the unblinded treatment allocation for the participant to allow dispensing. Pharmacy staff were assigned a different level of access to SCRAM to ensure that they were the only members of the local site team with access to the treatment allocation information.

Interventions

Investigational medicinal product details

Study treatment was supplied in capsules with dose levels as follows:

- amitriptyline – 25-mg capsules
- amitriptyline – 50-mg capsules
- duloxetine – 30-mg capsules
- pregabalin – 75-mg capsules
- pregabalin – 150-mg capsules
- matching placebo capsules.

Capsules were supplied in bottles containing nine, 23 or 51 capsules.

Participants were instructed to take medication orally before breakfast and at bedtime. Participants on dose levels 1 or 2 took one tablet in the morning and one tablet in the evening. Participants on dose level 3 took two tablets in the morning and two tablets in the evening. The placebo ensured that the same dosing schedule could be followed for each study drug. For example, a participant on dose level 1 of amitriptyline would take one placebo capsule in the morning and one 25-mg amitriptyline capsule in the evening. A participant on dose level 1 of standard dose pregabalin would take one 75-mg pregabalin capsule in the morning and one 75-mg pregabalin capsule in the evening. This ensured that the medication schedule appeared the same to participants, regardless of which medication they were currently taking.

The total daily dose of each drug was dependent on the dose level prescribed to the participant (*Table 1*). Participants were provided with clear instructions on the dosing schedule, and this was reinforced with written instructions and a medication diary.

Dose titration

Participants were titrated to a maximum tolerated dose level on starting each new treatment. The schedule for dose escalation was the same in each pathway (*Figure 2*).

When a new treatment was started, all participants started at dose level 1 and the dose was escalated slowly, one dose level at a time, towards a maximum tolerated dose or maximum permitted dose, whichever was reached first (see *Table 1*). Dose titration decisions were based on treatment response (i.e. 24-hour pain NRS score), side effect profile and participant preference. Dose titrations were

TABLE 1 Dosing schedule by dose level

Dose level	Amitriptyline	Duloxetine	Pregabalin (standard[a])	Pregabalin (reduced[b])
1				
a.m. dose	1 × placebo	1 × placebo	1 × 75 mg	1 × 75 mg
p.m. dose	1 × 25 mg	1 × 30 mg	1 × 75 mg	1 × placebo
2				
a.m. dose	1 × placebo	1 × 30 mg	1 × 150 mg	1 × 75 mg
p.m. dose	1 × 50 mg	1 × 30 mg	1 × 150 mg	1 × 75 mg
3				
a.m. dose	2 × placebo	2 × 30 mg	2 × 150 mg	2 × 75 mg
p.m. dose	1 × 25 mg &1 × 50 mg	2 × 30 mg	2 × 150 mg	2 × 75 mg

a Standard pregabalin doses to be used where latest eGFR result is ≥ 60 ml/minute.
b Reduced pregabalin doses to be used where latest eGFR result is 30–59 ml/minute.

Notes
Dose levels 1 and 2 = one tablet twice a day.
Dose level 3 = two tablets twice a day.

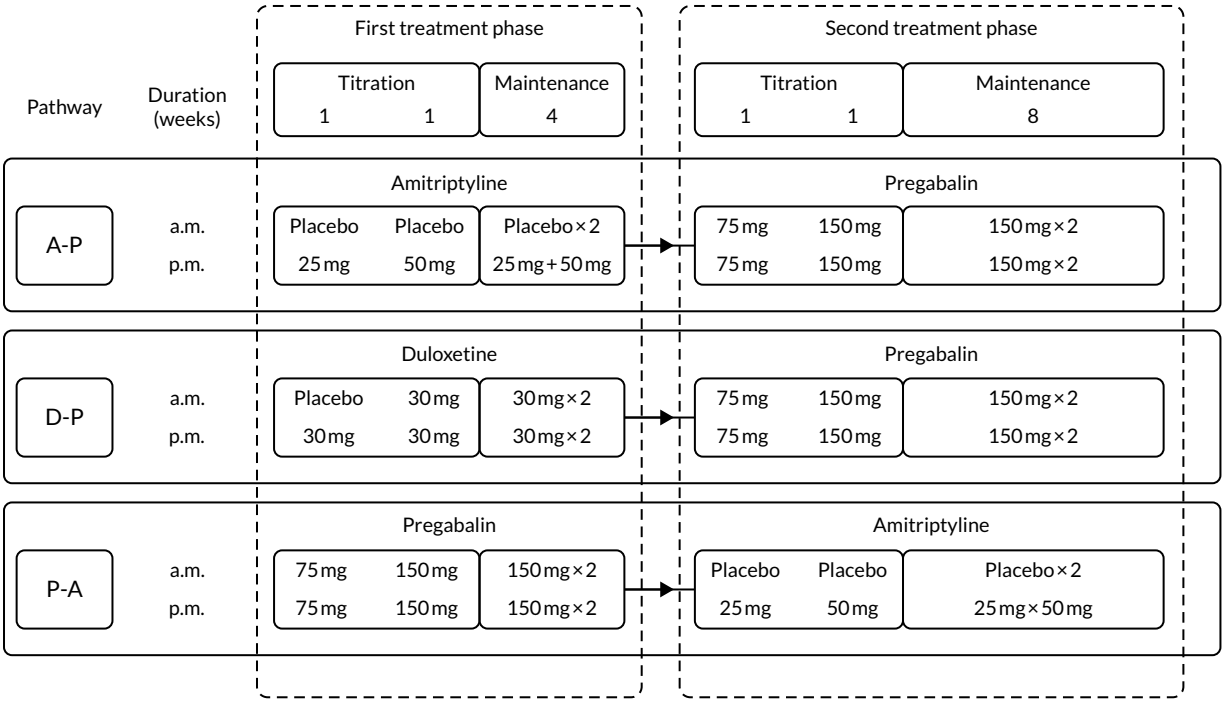

FIGURE 2 Dosing and titration schedule for treatment pathways. Each pathway had two treatment phases, each with a 2-week initial titration period towards maximum tolerated dose. Participants continued on maximum tolerated maintenance dose of the drug from the first treatment phase for the duration of the second treatment phase. For patients with an eGFR of ≤ 60 ml/minute, the maximum pregabalin dose was 300 mg/day.

usually made during the first 2 weeks of a new treatment; however, investigators were permitted to make dose changes at any time if deemed necessary. At weekly intervals, the site research nurse evaluated the participant's response to treatment and AEs and this information was used to guide dose titration.

Treatment response

Adequate pain relief was defined as a 24-hour pain NRS score of ≤ 3 for the purposes of dose titration decisions. Participants who experienced adequate pain relief at dose levels 1 or 2 did not have their dose escalated further.

Adverse events

Participants were asked to report all side effects. The local study team graded the side effects as mild, moderate or severe. The participant was asked to rate whether the side effects were tolerable or intolerable. If a side effect was rated as 'tolerable' and was non-severe, dose escalation was continued as indicated by the pain score assessment. However, sites were advised that if a patient was experiencing tolerable non-severe side effects, then it was also acceptable to maintain the current dose for a further week to allow side effects to improve before increasing the dose further. This decision was made by the local site team.

If side effects were severe or were rated as 'intolerable', then investigators considered reducing the dose by one dose level or discontinuing the medication based on the overall condition of the participant.

Participant preference

Participant preference was taken into account, where possible, when making dose titration decisions. However, the dose was not increased based on participant preference alone (i.e. the dose was increased only if the participant expressed a preference for an increase in dose and if this was indicated based on treatment response and side effect profile).

Treatment phases

Each treatment pathway was split into two treatment phases, as shown in *Figure 3*.

First treatment phase

During the first treatment phase, participants received monotherapy with the first-line treatment in the pathway. This lasted for a total of 6 weeks.

Responder/non-responder assessment

At the end of the first treatment phase, a decision was made either to continue on monotherapy or to start combination therapy with the addition of the second-line treatment in the pathway. This decision was based on the 7-day average pain NRS score during the week preceding the week 6 study visit. Participants were divided into 'responders' (with a pain score of ≤ 3 points) and 'non-responders' (with a pain score of > 3 points). Responders continued on monotherapy and non-responders commenced combination therapy.

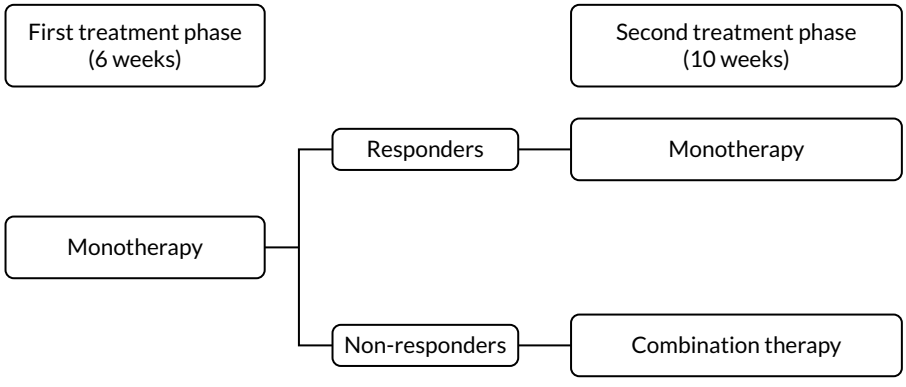

FIGURE 3 Two treatment phases per pathway.

Second treatment phase

The second treatment phase lasted for a total of 10 weeks. Responders continued on first-line treatment as a monotherapy for the remainder of the pathway. Non-responders commenced combination therapy, with the addition of the second-line treatment in the pathway, for 10 weeks.

Taper doses

At the end of a treatment pathway, participants were provided with a taper dose of their current medication. Participants were instructed to take the taper dose for 3 days and then to stop study medication completely for 4 days before commencing the next pathway. The taper dose was one dose level below the maximum tolerated dose, as shown in *Table 2*.

Where the patient experienced significant withdrawal side effects, the medication could be tapered down more gradually in accordance with the judgement of the investigator. However, the patient was still required to stop the medication completely for at least 4 days before starting the next pathway.

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

Permitted changes to the treatment schedule

To make the trial as pragmatic as possible, the following changes were permitted to the treatment schedule as needed:

- If there was significant intolerance to first-line treatment, participants were permitted to switch to the second-line treatment in the pathway as a monotherapy. This change could be made immediately at any time and without the need to wash out first-line treatment.
- Non-responders at week 6 who were on dose levels 1 or 2 of first-line treatment were permitted to increase the dose of first-line treatment rather than start combination treatment at the discretion of the local investigator.
- Second-line treatment could be added as a combination therapy up to week 13 if needed (e.g. if the participant was a responder at week 6, but then, subsequently, became a non-responder).
- For participants whose pain scores had not reduced at all at week 6, compared with baseline, or if their pain scores had increased first-line treatment was stopped and second-line treatment was started as a monotherapy for the remainder of the pathway.
- Participants who did not tolerate one treatment pathway could start the next treatment pathway early. In this case, the taper dose was dispensed early and the next pathway started following the appropriate washout period.

Compliance with intervention

Treatment compliance was assessed by the local study team at each study visit via pill counts and this was recorded on a treatment compliance log within the study database. Issues with compliance were discussed with participants and, if needed, participants were re-educated on the study requirements.

TABLE 2 Tapered dose levels

Maximum tolerated dose level	Tapered dose level
1	No taper dose required
2	1
3	2

Blinding and masking

The study was double-blinded, whereby participants and the local research team were blinded to treatment allocation, with the exception of the site pharmacist who was unblinded. Blinding was maintained with over-encapsulation 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. The IMP bottles were supplied with a tear-off label, which the centre's pharmacist removed prior to dispensing to the participants. Participants and sites were aware of whether monotherapy or combination therapy had been prescribed and of the dose level. Unblinding was considered only in the event of a medical emergency where knowledge of the participant's treatment allocation would change the clinical management. All participants were unblinded at the end of the study, when the final statistical report was completed.

Data collection and management

Data management was provided by the University of Sheffield CTRU who adhere to their own standard operating procedures relating to all aspects of data management, including data protection and archiving.

Participant confidentiality was respected at all times and the principles of the UK Data Protection Act[40] were followed. All participants were assigned a unique study identification number at screening that linked all of the clinical information held about them on the study database. Data were collected on standardised questionnaires and study-specific case report forms (CRFs) and were entered onto the CTRU's in-house data management system (Prospect). Access to Prospect was controlled by usernames and encrypted passwords, and a comprehensive privilege management feature was used to ensure that users had access to only the minimum number of data required to complete their tasks. This was used to restrict access to personal identifiable data. After data had been entered onto the database, electronic validation rules were applied on a regular basis and discrepancies were tracked and resolved. All entries and corrections were logged, with the person, date and time captured within the electronic audit trail.

Regular site monitoring visits occurred throughout the study and additional visits were undertaken where required. At these visits, the monitor reviewed activity to verify that the data were authentic, accurate and complete. Accurate and reliable data collection was assured by verification and cross-check of the CRFs against investigator's records (i.e. source document verification). The study monitor contacted and visited sites regularly to inspect CRFs throughout the study to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits also included a pharmacy visit to review processes, documentation and accountability of study drugs. CTRU staff reviewed entered data for possible errors and missing data points. A central review of consent forms was also completed, and sites were requested to post consent forms to CTRU on an ongoing basis. CTRU reviewed pharmacy dispensing logs for some patients centrally.

Study records will be stored for 25 years after the completion of the study before being destroyed.

Outcome measures

The study evaluated the superiority of at least one pathway in reducing the 7-day average 24-hour pain in patients with diabetic neuropathy.

Primary end point

Difference between 7-day average 24-hour pain (evaluated at patient level) among pathways on an 11-point NRS (0 = no pain and 10 = worst pain imaginable), measured during the final follow-up week of the treatment cycle (i.e. week 16). NRS 24-hour average pain is now considered the gold standard for the assessment of neuropathic pain and has been employed in almost all well-designed neuropathic pain studies over the past 10 years.[19,28,37]

Secondary end points

Efficacy

- Difference in 7-day average 24-hour pain (evaluated at patient level) on an 11-point NRS at week 6 among monotherapies.
- Difference in Short Form questionnaire-36 items (SF-36) physical mean scores (evaluated at patient level) at week 16 among pathways.[41]
- Difference in SF-36 physical mean scores (evaluated at patient level) at week 6 among pathways.[41]
- Difference in SF-36 mental mean scores (evaluated at patient level) at week 16 among pathways.[41]
- Difference in SF-36 mental mean scores (evaluated at patient level) at week 6 among pathways.[41]
- Difference in Hospital Anxiety and Depression Scale (HADS) mean anxiety scores (evaluated at patient level) at week 6 among pathways.[42]
- Difference in HADS mean anxiety scores (evaluated at patient level) at week 16 among pathways.[42]
- Difference in HADS mean depression scores (evaluated at patient level) at week 6 among pathways.[42]
- Difference in HADS mean depression scores (evaluated at patient level) at week 16 among pathways.[42]
- Difference in proportion of patients having treatment success (30%) at week 16 among pathways. Treatment success was defined as a reduction in 30% value at follow-up compared with baseline.
- Difference in proportion of patients having treatment success (50%) at week 16 among pathways. Treatment success was defined as a reduction in 50% value at follow-up compared with baseline.
- Difference in Brief Pain Inventory – Modified Short Form (BPI-MSF) measure of pain interference with function total score (evaluated at patient level) at week 6 among pathways.[43]
- Difference in BPI-MSF measure of pain interference with function total score (evaluated at patient level) at week 16 among pathways.[43]
- Difference in Insomnia Severity Index (ISI) total score (evaluated at patient level) at week 6 among pathways.[44]
- Difference in ISI total score (evaluated at patient level) at week 16 among pathways.[44]
- Difference in Patient Global Impression of Change (PGIC) (evaluated at patient level) at week 16 among pathways.[45]
- Difference in proportion of care pathway preferred by participants at week 50.

Cost-effectiveness

- The EuroQol-5 Dimensions (EQ-5D) is a routinely used generic HRQoL instrument. It is the instrument preferred by NICE for assessing HRQoL, and the newer five-level instrument [i.e. EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] is more sensitive than the original three-level version.[46]
- The Client Service Receipt Inventory (CSRI) is an instrument routinely used to capture health resource use and personal expenses. A modified version of the CSRI, where unnecessary questions were removed to reduce participant burden, was used.[47]

Safety

- The frequency and proportion of patients reporting at least one AE for each of the pathways. In addition, the relationship to intervention (i.e. definite, probable, possible, unlikely, unrelated or not assessable) was reported (frequency and proportion).
- The frequency and proportion of AEs for each of the pathways.

- A list of AEs for each of the pathways.
- The frequency and proportion of patients reporting at least one SAE for each of the pathways. In addition, the following characteristics were summarised (frequency and proportion): intensity (i.e. mild, moderate or severe), relationship (i.e. definite, probable, possible, unlikely, unrelated or not assessable), whether or not a suspected unexpected serious adverse reaction (SUSAR), whether or not resulted in death.
- Frequencies of SAEs for each of the pathways.
- A list of SAEs for each of the pathways.

Subgroup

- Neuropathic Pain Symptom Inventory (NPSI) questionnaire for subgroup analysis relating pain phenotype to treatment response.[48] There is emerging evidence that treatment response may be determined by a patient's pain phenotype.[49–51] In particular, the following outcomes were evaluated:

    - Difference in 'burning (superficial) spontaneous pain' NPSI mean subscores (evaluated at patient level) at week 6 among pathways.
    - Difference in 'burning (superficial) spontaneous pain' NPSI mean subscores (evaluated at patient level) at week 16 among pathways.
    - Difference in 'pressing (deep) spontaneous pain' NPSI mean subscores (evaluated at patient level) at week 6 among pathways.
    - Difference in 'pressing (deep) spontaneous pain' NPSI mean subscores (evaluated at patient level) at week 16 among pathways.
    - Difference in 'paroxysmal pain' NPSI mean subscores (evaluated at patient level) at week 6 among pathways.
    - Difference in 'paroxysmal pain' NPSI mean subscores (evaluated at patient level) at week 16 among pathways.
    - Difference in 'evoked pain' NPSI mean subscores (evaluated at patient level) at week 6 among pathways.
    - Difference in 'evoked pain' NPSI mean subscores (evaluated at patient level) at week 16 among pathways.
    - Difference in 'paresthesia/dysesthesia' NPSI mean subscores (evaluated at patient level) at week 6 among pathways.
    - Difference in 'paresthesia/dysesthesia' NPSI mean subscores (evaluated at patient level) at week 16 among pathways.
    - Difference in NPSI mean total scores (evaluated at patient level) at week 6 among pathways.
    - Difference in NPSI mean total scores (evaluated at patient level) at week 16 among pathways.

Patient's perceived tolerability

- Difference in tolerability among pathways, evaluated at the patient level on an 11-point NRS at week 6.
- Difference in tolerability among monotherapies, evaluated at the patient level on an 11-point NRS at week 6

Changes to subgroup analyses and exploratory analyses

The study had intended to characterise pain phenotype by the individual domains of the NPSI; however, a new classification system for pain based on the NPSI was used instead.[52] In addition, the following subgroups were investigated: age, pain score at baseline, anxiety and depression scores at baseline, previous medication and the COVID-19 lockdown restrictions. Additional analyses were performed to compare outcomes among patients on combination therapy against those who remained on monotherapy.

Economic evaluation

A within-trial economic evaluation was completed as part of the study to understand the relative cost-effectiveness of the three treatment pathways.

Data collection tools

A pro forma of each of the forms was available to be used as source documents if needed. These forms were provided to each site electronically, along with a paper copy of each form for reference.

Procedures for assessing efficacy

Numeric Rating Scale 24-hour average pain was assessed via pain diaries that were given to participants at each study visit. Participants were instructed to complete the diaries each morning during the study. Completed diaries were then collected at the subsequent visit. During the weekly telephone calls, the research nurses reminded participants to record their pain scores every day. Pain scores were also collected via daily text messages where participants had given additional consent for this.

Procedures for assessing safety

The following safety assessments were performed to assess safety:

- Blood tests were performed at week 16 of each pathway.
- Vital signs were assessed at week 16 of each pathway.
- AEs were assessed during each study visit or telephone call.
- Concomitant medications were reviewed during each study visit or telephone call.

Additional procedures for assessing neuropathic pain

The NPSI and BPI-MSF were completed to assess neuropathic pain.

Procedures for assessing quality of life, psychological well-being and health economics

The following questionnaires were completed to assess QoL:

- ISI
- HADS
- SF-36
- EQ-5D-5L
- modified CSRI
- Pain Catastrophizing Scale
- Suicidal Risk Questionnaire
- PGIC
- Tolerability Scale.

Questionnaires could be completed during the visit. Alternatively, questionnaires could be posted to participants in advance of the visit and participants could bring the completed questionnaires when they attended their study visit. In the event that the participant forgot to bring the questionnaires or had not completed them, they were provided with another copy to complete during the visit.

Study-related case report forms

The following additional CRFs were completed by the investigators or delegates (i.e. sub-investigators delegated to consent or collect data) during the study:

- pre-screening log
- screening consent

- demographics
- medical history
- mTCNS
- DN4
- previous medications
- weekly contact form
- pregnancy test
- confirmation of eligibility
- randomisation
- treatment decisions
- treatment compliance log
- unblinding
- unscheduled dose changes
- pregnancy information
- protocol non-compliance
- intervention withdrawal
- study completion discontinuation.

See *Appendix 1* for the CRF completion schedule and *Appendix 2* for the questionnaire completion schedule.

Ancillary substudies

Participants were given the opportunity to consent to blood sample collection for future research. This aspect of the study was optional, and participants could take part in the main study without consenting to the blood sample collection. Samples were obtained at the same time as other study blood samples (i.e. week −2 or week 16 of each pathway) and shipped directly to the central labs via Royal Mail (Royal Mail Group plc, London, UK).

Patient and public involvement

Patient and public involvement (PPI) representatives have been involved throughout the study, including involvement in the initial study design, as well as implementation and oversight. The Diabetes PPI Panel at Sheffield Teaching Hospitals NHS Foundation Trust reviewed the study at the proposal stage. The PPI representatives were supportive of the proposal, including the study design, and they contributed to the choice of end points for the study. The panel was later involved in the development of the patient information sheet, consent form and study medication diary, helping to ensure that the study documents were accessible for potential participants. The Trial Steering Committee (TSC) included a PPI representative who provided ongoing input into the oversight of the study. PPI representation on the TSC ensured that the patient perspective was considered throughout the trial, including in decision-making regarding protocol amendments and trial recruitment strategies.

Trial management and oversight

Trial Management Group

The Trial Management Group (TMG) consisted of the chief investigator, collaborators, site investigators, site research nurses and staff from Sheffield CTRU. The TMG was responsible for the day-to-day implementation of the trial.

Data Monitoring and Ethics Committee

A Data Monitoring and Ethics Committee (DMEC) consisted of an independent statistician and two independent clinicians with research expertise. The DMEC reviewed reports provided by Sheffield CTRU to assess the progress of the study, the safety data and the critical end-point data. The DMEC provided feedback to the TSC following each meeting. The chief investigator (or delegate) and members of staff from Sheffield CTRU attended the open sessions of the DMEC meetings as observers. An unblinded statistician from Sheffield CTRU produced the report and attended the closed sessions of the DMEC.

Trial Steering Committee

The TSC consisted of independent clinicians, an independent statistician and a PPI representative. The role of the TSC was to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and to consider the recommendations from the DMEC. The chief investigator (or delegate), a sponsor representative and members of staff from Sheffield CTRU attended the TSC meetings as observers. Sheffield CTRU produced reports for review during the TSC meetings.

Changes to the protocol

All protocol amendments are listed in *Appendix 3*. A summary of the key changes is provided below.

Eligibility criteria

In substantial amendment 1, the inclusion criteria were updated to clarify that patients must have neuropathic pain affecting both feet and to update the Toronto Clinical Neuropathy Score to the 'modified' version.[39] The exclusion criteria were updated to allow investigator judgement to be used when assessing the criteria for alcohol/substance abuse, history of psychiatric illness and prostate hypertrophy or urinary retention. The permitted dose of morphine equivalent was reduced from 120 to 100 mg/day. The exclusion criterion relating to history of ischaemic heart disease was updated to exclude any patient who had suffered a recent myocardial infarction (< 6 months prior to randomisation). New exclusion criteria were added for major amputations of the lower limbs and active diabetic foot ulcers.

Substantial amendment 7 updated the requirements for neuropathic pain to allow the pain to be present in the feet and/or hands. The exclusion criteria were also updated to clarify that only patients with non-diabetic symmetrical polyneuropathies were excluded. Previously, any non-diabetic neuropathy was an exclusion criterion, for example patients with diabetic neuropathy and carpal tunnel syndrome would previously have been excluded from the trial, but this was not the intention. This point was clarified in substantial amendment 7 to ensure that patients were not excluded unnecessarily. The exclusion criterion relating to liver function tests was updated to clarify that only the AST/ALT results were relevant for the eligibility assessment. The exclusion criterion relating to the electrocardiography results was updated to clarify that patients with a current history of arrhythmia were not eligible for the trial.

In substantial amendment 8, the exclusion criteria were updated to allow patients taking concomitant SSRIs to join the study provided that they had prior concomitant and safe use of SSRIs with the study medication (duloxetine and/or amitriptyline). The exclusion criterion relating to active foot ulcers was also updated to allow for investigator discretion. Patients were only excluded if the investigator felt that the ulcer would have a confounding or detrimental effect on the primary outcome or on patient participation.

To minimise the amount of time participants were on no pain medications, substantial amendment 12 allowed participants to be randomised early if the pain scores were high, provided that the mean pain score for the week was > 4 points. The exclusion criterion for heart failure was updated to exclude

patients with heart failure class III or above (rather than class II or above). The exclusion criterion for postural hypotension was also updated to allow investigator discretion in the decision. Previously, all patients with a postural drop of > 20 mmHg were excluded.

In substantial amendment 13, the exclusion criteria were updated to clarify that patients taking concomitant citalopram were not eligible for the study. In addition, an update was included to exclude patients with second- or third-degree heart block or left bundle branch block (patients with right bundle branch block or first-degree heart block were permitted to be included following discussion with the cardiology team).

Data collection for the primary end point

At an early meeting, the TSC noted that there were potential issues with recording pain scores using paper diaries, including retrospective completion. The TSC recommended that the trial team consider an alternative method for collecting the primary end-point data. A text message data collection system was included in substantial amendment 5 and implemented in January 2018. This allowed daily text messages to be sent to participants who had provided optional consent for this aspect of the study. The text messages reminded participants to take their study medication and asked them to reply with their pain score, allowing the scores to be captured in real time.

Study treatment

Substantial amendment 1 allowed participants to start the next treatment pathway early if they wanted to withdraw from their current treatment pathway. The requirements for performing a dose review (i.e. to reduce the dose or discontinue a drug) were updated in substantial amendment 2, and it was clarified that only side effects that were severe or intolerable would require a dose review (rather than side effects which were moderate).

In substantial amendment 5, a reduced pregabalin dosing schedule was introduced for participants with an eGFR of 30–59 ml/minute. This ensured that the protocol was in line with *British National Formulary* (BNF) guidelines for pregabalin dosing.[53] Substantial amendment 5 also allowed participants to start second-line treatment up to week 13 if needed.

Substantial amendment 7 clarified that participant preference could be considered when making dose titration decisions.

In substantial amendment 8, an update was made to allow study medication to be tapered more gradually between pathways in the event of significant withdrawal side effects, at the discretion of the local investigator.

Statistical methods

Sample size

A mean change between groups of 0.5 points was chosen based on the effect size previously reported in a crossover study[29] for comparison of two active interventions for neuropathic pain. It was estimated that this would equate to an 8% difference between groups in the proportion of people improving by at least 1 point,[54] which is considered a minimally clinically significant change in an individual.[55] By using a within-patient standard deviation (SD) of 1.65,[3,9] an alpha of 0.0167 to allow for three comparisons and 90% power, it was calculated that 294 evaluable participants were required.[56]

The original plan was to screen 536 patients, in total, for participation in the study. Assuming a 25% dropout rate, the study intended to recruit and randomise 392 participants to ensure that 294 participants completed the study.

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[29,31,57] had used a 1 NRS point difference. With approval from the TSC, our PPI 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 alpha of 0.0167), the trial would achieve 90% power to detect a difference of 1 NRS point, assuming at least 74 patients per arm provided outcome data. With a 25% dropout, as originally assumed, the trial would have 95% power to detect a 1-point change and was sufficient to estimate differences in average pain to within a standard error of 0.25 NRS points.

Statistical analysis

General principles

Analyses were limited to randomised and eligible participants who started their pathway. Any participant who withdrew from study in one pathway was excluded from any succeeding pathways. 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. Statistical comparisons used 98.3% confidence intervals (CIs) and a 0.0167 statistical significance level was used for pairwise comparisons. Analyses were undertaken using intention-to-treat principles, which evaluated the policy of pathways rather than adherence to therapies. All analyses were undertaken using Stata® version 16 (StataCorp LP, College Station, TX, USA).

Treatment uptake and response

Treatment uptake was summarised separately for first- and second-line therapies as (1) the proportion of participants stopping treatment prior to week 16 and (2) the dose level being taken at the end of the pathway at week 16 among those on therapy. The uptake of second-line therapy was further categorised as (1) being in combination with first-line therapy or (2) as a switch from first-line monotherapy.

Treatment response at week 6 was defined in relation to first-line monotherapy. A patient was classified as a treatment responder if they remained on first-line monotherapy at the week 6 visit with an average pain score of ≤ 3 points over the previous 7 days. Conversely, non-responders were those who (1) discontinued first-line monotherapy for AE, toxicity or ineffectiveness on or prior to week 6, (2) started second-line treatment (as combination therapy or as treatment switch) on or prior to week 6 or (3) had a NRS pain score > 3 points at week 6.

Treatment response at week 16 was in relation to both therapies. Patients who remained on at least one study medication and reported a 7-day average NRS score of ≤ 3 points were defined as having responded to the pathway, whereas those who discontinued for AE, toxicity or poor effectiveness and/or had a NRS score > 3 points were classed as non-responders.

Numeric Rating Scale pain

Self-reported NRS scores were collected daily for the duration of the pathway, by short message service (SMS) and/or via patient diaries. On days when a participant had provided both SMS and diary data, the NRS was taken from the SMS. A weekly average was calculated only if NRS scores were available on at least 4 out of the 7 days. The time window for the 6-week outcome was −2 weeks to + 1 week (i.e. any consecutive 7-day period ending between 28 and 49 days post commencement), provided that this did not extend to the washout phase or the next pathway. The week 16 data time window was −3 weeks to + 1 week (i.e. any consecutive 7-day period ending between 91 and 119 days post commencement), again, provided that this did not extend to the washout phase or next pathway.

At weeks 6 and 16, NRS scores were analysed using linear mixed-effect modelling. The binary outcomes (i.e. 30% pain reduction from baseline, 50% pain reduction from baseline and NRS score of ≤ 3 points)

were analysed by logistic mixed effects regression. Baseline NRS score was the pain score taken during the washout period (i.e. week –1) immediately prior to randomisation and changes from baseline were calculated in reference to this score.

Missing data

The primary analysis was performed using a mixed model on complete-case data, which may be inadequate in situations where differential levels of withdrawal (or differential reasons for withdrawal) occur between groups. To address this, the following three sensitivity analyses were undertaken, using statistical imputation to assess the impact of missing data on pain scores:

1. Last observation carried forward, using the last available weekly NRS data. Although this approach has been widely criticised as oversimplistic,[58] it offers a conservative estimate of the treatment effect in the case of conditions that improve with time.[59]
2. Multiple imputation,[60] which is unbiased under the missing at random assumption if missing data can be predicted by the imputations model's characteristics.
3. Controlled multiple imputation,[61] in which informative withdrawal had more pessimistic values imputed.

Approach 2 used chained predicted mean matching imputation, with 10 nearest neighbours and 100 imputations. Missing data were imputed based on age, sex, baseline total NPSI score, treatment arm, pathway and any previous weekly NRS data available. Trace plots were used to assess convergence and, on the basis of these, 1000 burn-in imputations were used.

Approach 3 assumed that the participants who withdrew from treatment because of toxicity and/or inadequate treatment response would have a worse response than the value imputed by multiple imputation. Specifically, the imputed NRS values y_i^* created by step 2 were replaced with a pessimistic imputation ($y_i^* + \delta$), with δ ranging between 0.5 and 2.5. Imputed values were bounded at 10 where applicable.

Subgroups

The NRS responses were analysed in relation to the age, baseline pain, HADS anxiety and depression scores and pain phenotypes, as derived from NPSI scores.[52] Additional post hoc analyses were undertaken to assess whether or not outcomes were temporally associated with the COVID-19 lockdown, which began 3 months before the last patient last visit. Subgroup analyses were undertaken by adding an interaction term to the model and reported as marginal means.

Preferred treatment

After completing all three pathways, participants were asked to choose their preferred treatment. This was reported as a single 3 × 1 contingency table. The hypothesis test of equal proportions was assessed by chi-squared test.

Other efficacy assessments

All other efficacy assessments were undertaken at 6 and 16 weeks after the start of the treatment pathway, which corresponded to the end of monotherapy phase and the end of the treatment pathway.

Harms

Adverse events were recorded at each follow-up visit and categorised prior to unblinding. Any AEs occurring prior to the first treatment pathway were excluded. AEs were presented as the number of patients experiencing each event type and the number of events of each type. Where data allowed, the proportions were compared between arms using a mixed-effect logistic regression approach, as per binary pain outcomes. The following summaries were presented:

- all AEs
- all AEs of moderate or severe intensity and related (probably or definitely) to either treatment
- all SAEs.

Additional post hoc analysis looked at the number of days affected by each event type and the treatment phase during which the event occurred.

Health economic methods

A within-trial cost–utility analysis was conducted alongside the clinical study. The cost–utility analysis estimated the mean differences in costs, QALYs and the incremental cost-effectiveness ratio (ICER) over 16 weeks for each treatment pathway. The cost–utility analysis was conducted in line with the NICE *Guide to the Methods of Technology Appraisal*[62] and is in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[63] The analysis is presented from an NHS and Personal Social Services perspective.

Quality of life and quality-adjusted life-years

Quality-adjusted life-years were measured over the 16-week period using the EQ-5D-5L.[64] The EQ-5D-5L is a preference-based QoL measure that can be used in economic evaluations. The EQ-5D-5L consists of five dimensions (mobility, self-care, usual activities, pain or discomfort and anxiety or depression). For each dimension, responders indicate which of five levels their health is at today, with levels ranging from no problems to unable to do/extreme problems. Responses are then scored on a 0–1 scale on which 0 represents death, 1 represents perfect health and negative values indicate states worse than death.

In the OPTION-DM study, and in line with NICE guidelines,[65] preference weights were obtained from van Hout *et al.*'s[66] mapping study in the main analysis, with Devlin *et al.*'s[46] preference weights applied in sensitivity analysis.

Participants completed the EQ-5D-5L at baseline, prior to the study commencing, and at 6 and 16 weeks in each treatment pathway. Given that this was a crossover study and participants received all three treatment pathways in turn, for the treatment pathway received second or third in order it was assumed that participants' EQ-5D scores returned to the baseline value during the washout period between treatment pathways. Area under the curve using the trapezium rule was then used to estimate QALYs, which are presented in years throughout this report.

Resource use

NHS resource use was measured for each participant between baseline and the final follow-up (i.e. before crossover/end of follow-up). Resource use included all medication costs, visits to health services and any social care and community support. Medical costs were taken from the study medication records. In addition, other NHS resources used were self-reported by participants using the widely used and validated CSRI questionnaire.[47] Unnecessary questions in the CSRI were removed to reduce the burden for participants; however, questions relating to personal costs incurred and time off work (where relevant) were retained for sensitivity analysis.

Details of unit costs for hospital visits, general practitioner (GP) visits, and social and other health-care services are listed in *Table 3* (further details are available from the authors by request). Unit costs for laboratory tests were obtained from the national cost collection for the NHS[67] and unit costs for medications are taken from the BNF.[53] For unit costs to be applied to the same year, medication costs were deflated back to 2018/19 prices using the inflation rates provided in the Personal Social Services Research Unit (section 15.2).[76]

Treatment costs

Treatment costs consisted of the costs of medication (i.e. amitriptyline, duloxetine and pregabalin), the cost of the clinic visit (face to face or via telephone) and the cost of laboratory tests. *Table 4* lists the treatment costs and the source of unit costs. Treatment medication was costed as it would be delivered within the NHS (rather than during a research study) so that results are presented from an

TABLE 3 Sources of reference costs

Resource	Source	Unit cost (£)
A&E visit	The *National Cost Collection for the NHS* (2018/19):[67] index sheet unit cost for accident and emergency	166.00
Hospital admissions	The *National Cost Collection for the NHS* (2018/19):[67] index sheet unit costs averaged for elective and non-elective inpatients	3477.36
Outpatient visits	The *National Cost Collection for the NHS* (2018/19):[67] total outpatient attendance sheet	127.00
GP home/surgery visit	Curtis and Burns (section 10.5)[68]	39.00
GP telephone call	Curtis and Burns (section 10.5)[68]	15.52
Practice nurse	Curtis and Burns (section 10.2)[68]	42.00
Practice nurse telephone call	Curtis and Burns (section 10.5)[68]	7.80
Prescription costs	Curtis and Burns (section 10.4)[68]	1.30
Home help	Curtis and Burns (section 11.5)[68]	28.00
Social worker	Curtis and Burns (section 11.1)[68]	51.00
Community pain management	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	116.00
Physiotherapy	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	55.00
Occupational therapy	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	66.00
Podiatry NHS	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	51.00
Podiatry private	Averaged across The Podiatry Clinic,[69] A&A Podiatrists[70] and the Footcare Centre[71]	54.50
Psychology	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	79.00
Diabetic clinic	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	195.00
Psychiatrist	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	203.00
Counsellor	Agenda for Change 2018/19 (mid-point band 6)[72]	17.37
Eye clinic	The *National Cost Collection for the NHS* (2018/19):[67] non-CL WF01A	88.00
Vascular surgery	The *National Cost Collection for the NHS* (2018/19):[67] day case	66.00
Aromatherapy	Averaged across Escape Holistic Therapies,[73] Holly's Holistics[74] and Natural at Heart[75]	50.00

A&E, accident and emergency; PSSRU, Personal Social Services Research Unit.

TABLE 4 Treatment costs and unit cost sources

Treatment	Unit cost source	Unit cost (£)
Amitriptyline 25 mg: 28 tablets	BNF[53]	0.92
Amitriptyline 50 mg: 28 tablets	BNF[53]	1.68
Duloxetine 30 mg: 28 tablets	BNF[53]	1.63
Pregabalin 75 mg: 56 capsules	BNF[53]	2.12
Pregabalin 150 mg: 56 capsules	BNF[53]	2.94
Diabetic outpatient clinic: face to face	The *National Cost Collection for the NHS* (2018/19):[67] CL WF01A	145.00
Diabetic outpatient clinic: telephone	The *National Cost Collection for the NHS* (2018/19):[67] CL non-face to face WF01A	86.00
Laboratory tests (i.e. liver function, blood count, HbA_{1c}, creatinine, eGFR, urea, electrolytes)	The *National Cost Collection for the NHS* (2018/19):[67] pathology services	328.00

NHS perspective. For example, the smallest pack of amitriptyline 25-mg tablets contains 28 tablets, and so the medicine cost at the week 1 visit was £0.94. The frequency of study medication visits were assumed to mirror what would take place in an NHS setting and these were either face to face or via telephone. Laboratory tests were assumed to take place once at the beginning of each treatment pathway and were costed accordingly.

As this was a crossover study, the time period in which the participants received the different treatment pathways could affect resource use and QoL. Therefore, linear regression analysis was performed to establish whether or not there was a difference in costs depending on the time period the participant received the treatment pathway. A separate regression model was fitted to costs and QALYs per treatment pathway (i.e. A-P, D-P and P-A). Confidence intervals around the coefficients for differences in costs between those receiving a treatment pathway first and either second or third in order were calculated using 5000 bootstrap simulations. A p-value of < 0.05 was used to establish statistical significance of an ordering affect. If statistical significance was established, then a sensitivity analysis would be carried out to allow for the time period in which participants received the treatment pathway.

Costs are reported using the 2018/19 time frame.

Cost-effectiveness analysis

Results are presented as a within-trial analysis, using a pairwise ICER as cost per QALY gained. It is possible to present this analysis because, within the crossover trial, participants received all three treatments. A non-pairwise (conventional) ICER as cost per QALY gained is also presented. Three cost-effectiveness comparisons are carried out: (1) A-P compared with D-P, (2) A-P compared with P-A and (3) D-P compared with P-A. Results are presented on the cost-effectiveness plane and on cost-effectiveness acceptability curves. No discounting was applied, as the follow-up period was < 1 year.

A total of 5000 simulations were used to obtain 95% CIs using bootstrapping.

All analysis was undertaken using Stata.

Sensitivity analysis

To allow for uncertainty, the following sensitivity analyses were undertaken:

- Devlin *et al.*'s[46] algorithm for EQ-5D-5L utility values was used as an alternative to van Hout *et al.*'s[66] algorithm for utilities.
- Analysis was undertaken with a wider societal perspective for costs. Personal costs and time off work are included, as reported by participants using the CSRI questionnaire. Participants provided details of any out-of-pockets costs related to employing extra help, transport to health-care appointments, modifications to their home and equipment purchased as a result of their condition. Details were also provided on any time away from usual activities for themselves or for friends or relatives as a result of their condition. Participant and friend/relative time was costed at the average UK wage as detailed in the Office for National Statistics annual survey for hours and earnings (2019).[77]
- EQ-5D responses were missing for 27–32% of participants. Therefore, multiple imputation[58] was carried out to impute the missing values assuming responses were missing at random. As with the statistical analysis, predicted mean matching with 10 nearest neighbours and 100 imputations were carried out. Missing data were imputed base on age, sex and treatment pathway.

Chapter 3 Results

Participant recruitment

Figures 4 and *5* detail the patient flow through the study by treatment (i.e. A-P, D-P and P-A) and by chronological treatment pathway (first, second and third). Participating sites collected pre-screening data on all patients who the site had been in contact with regarding the study. Between 2 October 2017 and 31 July 2019, 1004 patients were identified as being potentially eligible for the trial across 18 secondary care hospital centres (a further three centres were activated to recruitment, but did not identify any potential participants). Of these patients, 426 were ineligible. The main reasons for ineligibility at this stage were not having neuropathic pain ($n = 202$), contraindications for study medications ($n = 42$), having other painful medical conditions ($n = 39$) and use of prohibited concomitant treatment ($n = 28$). A further 314 patients were not interested or unable to continue into the study, with the main reasons being that they were unable or unwilling to attend all study visits ($n = 146$) or were not wanting to come off current treatment ($n = 76$). Twelve patients did not continue for other reasons.

Between 2 October 2017 and 31 July 2019, 252 patients attended the consent visit at week −2 across 17 trial centres, and 222 of these patients provided informed consent. Of those patients who consented, 40 discontinued from the trial before randomisation and a further 42 were ineligible because of unconfirmed or low levels of neuropathic pain ($n = 37$) or clinically significant arrhythmia ($n = 5$). One hundred and forty patients proceeded to be randomised at week 0 across 13 sites. Ten patients were excluded following randomisation and within the first treatment pathway. Six patients provided no post-baseline data (three withdrew citing the trial burden, two were lost to follow-up and one developed a significant comorbidity) and four were randomised in error.

A total of 53 patients withdrew from the study before completing all three treatment pathways. The majority ($n = 33$) of withdrawals came in the first pathway, with a further 13 withdrawals in pathway 2 and seven withdrawals in pathway 3. The numbers of patients starting first, second and third pathways were 130, 97 and 84, respectively, and the numbers of patients contributing 7-day pain scores at week 16 were 105, 85 and 74, respectively.

Recruitment was originally expected to be completed within 12 months by eight trial centres. Owing to slow recruitment rates, the total number of centres was increased to 21 and a number of changes were made to the eligibility criteria and study processes to improve recruitment (see *Chapter 2*, *Changes to the protocol*). In addition, assistance was provided to participating centres via regular teleconferences, recruitment packs and one-to-one discussions with the research fellow based at the lead site in Sheffield.

Protocol non-compliances

A total of 146 (major, $n = 73$; minor, $n = 73$) protocol non-compliances were reported during the trial and no serious breaches were reported. Five participants were ineligible and were withdrawn from the trial during the first treatment pathway. One participant did not contribute primary outcome data as a result of a good clinical practice non-compliance in the recording of the data at site.

As the study medication was provided in up to eight blinded medication bottles, the dosing schedule for participants was more complicated than in usual care. Thirty-seven cases of participant non-compliance with treatment were reported. These included the participant taking more/less medication than prescribed or taking medication from incorrect bottles.

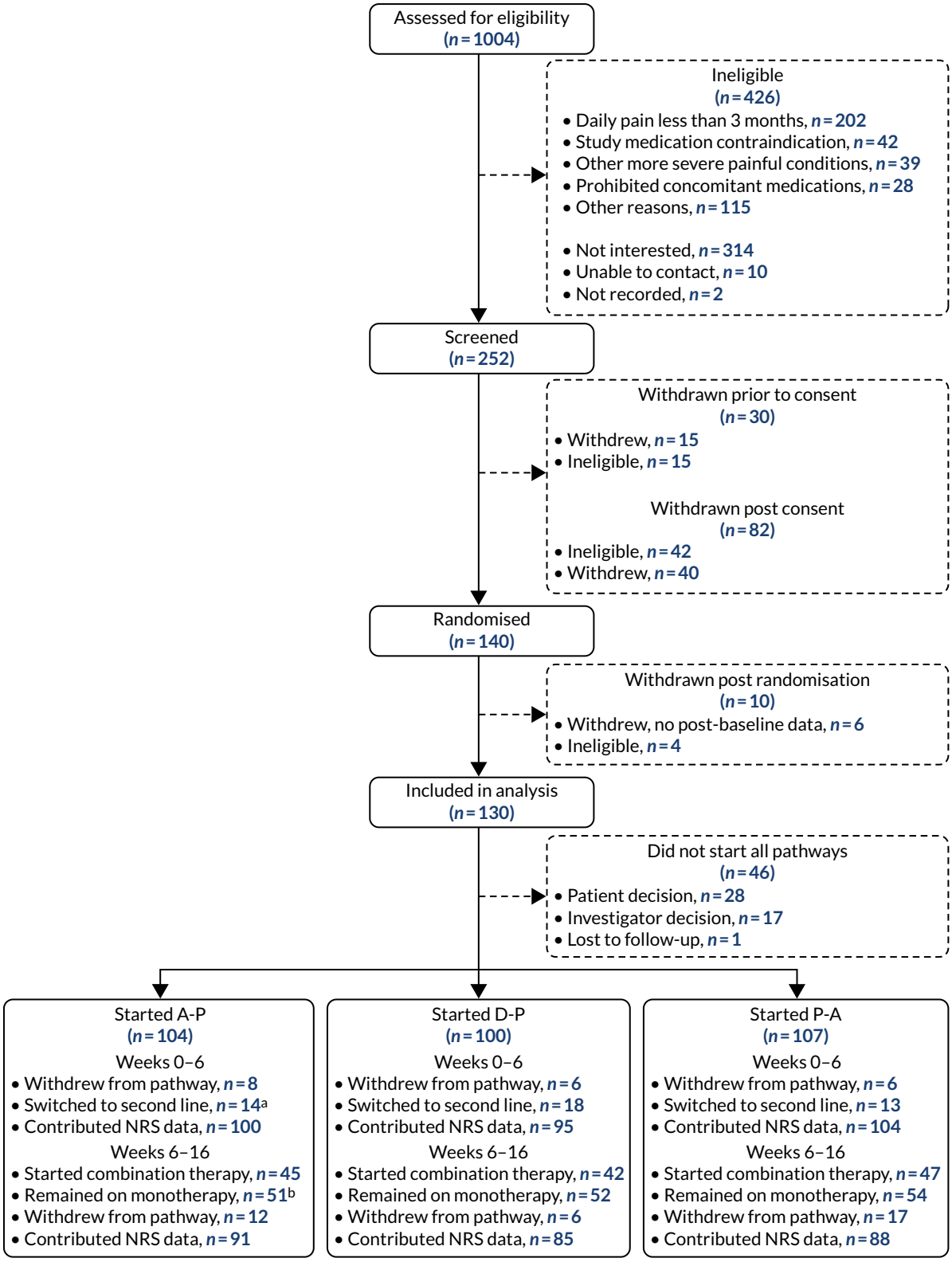

FIGURE 4 Patient disposition and study flow chart. a, Switch to second-line monotherapy before week 6; and b, includes switches to second-line monotherapy after week 6.

Fifty-nine non-compliances were reported in relation to trial treatment or procedural issues and this included 22 cases where a patient was prescribed and/or dispensed an incorrect dose of medication. To our knowledge, the errors in treatment doses did not result in any AEs.

Three non-compliances were reported in relation to on-site visits being missed due to COVID-19 restrictions.

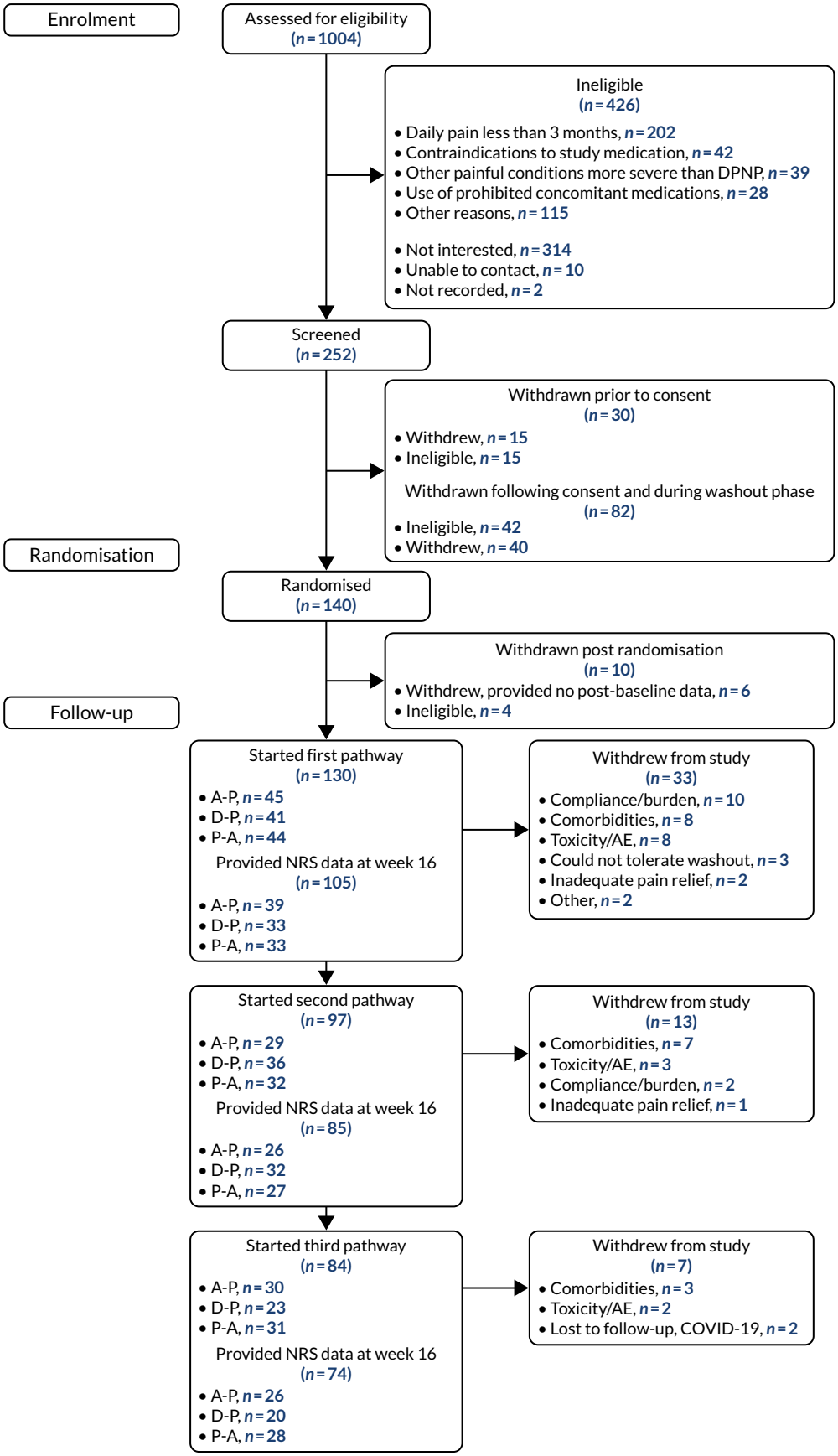

FIGURE 5 Patient disposition and study flow chart by chronological treatment pathway.

Characteristics of trial participants

Trial participants were of similar age to screened patients (median 61.8 years vs. 61.2 years), but fewer females were enrolled (26% vs. 41%).

The full characteristics of the 130 trial participants are presented in *Table 5*, split according to whether or not the patient completed the three treatment pathways. The majority (82%) of patients had type 2

TABLE 5 Demographics and baseline characteristics

Characteristic	Completers (*N* = 77)	Non-completers (*N* = 53)	Total (*N* = 130)
Demographics			
Age (years), mean (SD)	61.3 (10.9)	62.5 (11.2)	61.8 (11.0)
Female, *n* (%)	22 (29)	12 (23)	34 (26)
BMI (kg/m^2), mean (SD)	31.7 (6.3)	31.7 (7.0)	31.7 (6.6)
Diabetes characteristics			
Type 1, *n* (%)	12 (16)	10 (19)	22 (17)
Type 2, *n* (%)	63 (82)	43 (81)	106 (82)
Type missing, *n* (%)	2 (3)	0	2 (2)
HbA_{1c} (mmol/mol), mean (SD)	65.4 (13.2)	68.4 (17.2)	66.6 (15.0)
Duration of diabetes (years), mean (SD)	14.9 (9.0)	15.6 (9.7)	15.1 (9.3)
Duration of neuropathic pain (years), mean (SD)	4.8 (4.1)	5.0 (4.1)	4.9 (4.1)
Previous medication use, *n* (%)			
Amitriptyline	30 (39)	19 (36)	49 (38)
Pregabalin	27 (35)	18 (34)	45 (35)
Duloxetine	28 (36)	19 (36)	47 (36)
Gabapentin	27 (35)	17 (32)	44 (34)
Any opioid	27 (35)	20 (38)	47 (36)
Pain characteristics, mean (SD)			
NRS pain (0–10; higher scores indicate greater pain)	6.7 (1.5)	6.5 (1.4)	6.6 (1.5)
BPI-MSF (0–10; higher scores indicate greater pain)			
Pain severity score	6.1 (1.6)	6.1 (1.9)	6.1 (1.7)
Pain interference score	5.8 (2.3)	6.1 (2.5)	5.9 (2.4)
NPSI (0–10; higher scores indicate greater pain)			
Superficial spontaneous burning pain	6.0 (2.8)	6.0 (3.1)	6.0 (2.9)
Deep spontaneous pressing pain	4.8 (2.8)	4.7 (2.7)	4.8 (2.8)
Paroxysmal pain	5.3 (2.9)	5.8 (2.9)	5.5 (2.9)
Evoked pain	4.6 (2.5)	3.9 (2.8)	4.3 (2.6)
Paraesthesia/dysaesthesia	6.3 (2.4)	6.4 (3.0)	6.3 (2.7)
NPSI total score (0–100; higher scores indicate greater pain)	52.6 (18.1)	52.1 (21.6)	52.4 (19.5)

BMI, body mass index.

diabetes, had experienced neuropathic pain for an average of 5 years (median duration 3.4 years, range 4 months to 25 years) and self-rated their pain at 6.6 points out of 10 points (NRS) and 6.1 points out of 10 points (BPI-MSF). Patients more commonly described their pain as relapsing/remitting as opposed to deep or involved (NPSI) and one-third of participants reported having taken each of amitriptyline, pregabalin, duloxetine and gabapentin at some point prior to trial entry.

Trial medication usage

The study treatment use is summarised in *Table 6*. The uptake of first-line therapy was similar for each arm, with around half of patients remaining on the highest dose at the end of each pathway.

TABLE 6 Study treatment use

Treatment use	Pathway			*p*-value
	A-P	D-P	P-A	
Started treatment pathway, *n*	104	100	107	
First-line therapy				
Average dose (mg)/day at week 6	56	76	397	
Number (%) on highest dose	53 (51)	46 (46)	59 (55)	
Number (%) discontinuing first-line therapy				
Discontinued at any time (0–16 weeks)[a]	29 (18)	29 (24)	32 (20)	0.928
Because of AE/toxicity	11 (11)	17 (17)	5 (5)	0.031
Because of poor response	10 (10)	9 (9)	14 (13)	0.518
Because of other reasons	8 (8)	3 (3)	13 (12)	
Discontinued while on monotherapy[b]	25 (24)	25 (25)	23 (21)	0.797
Because of AE/toxicity	9 (9)	14 (14)	5 (5)	0.087
Because of poor response	10 (10)	9 (9)	12 (11)	0.851
Because of other reasons	6 (6)	2 (2)	6 (6)	
Second-line therapy				
Number (%) started	60 (58)	61 (61)	60 (56)	
Started as combination therapy	45 (43)	42 (42)	47 (44)	
Switched from first line	15 (14)	19 (19)	13 (12)	
Average dose (mg)/day at end of study	347	405	52	
Number (% of started) on highest dose	21 (47)	23 (55)	2 (47)	
Number (% of started) discontinuing second-line therapy				
Discontinued at any time[c]	13 (22)	7 (11)	18 (30)	0.123
Because of AE/toxicity	4 (7)	3 (5)	9 (15)	0.383
Because of poor response	6 (10)	2 (3)	4 (7)	0.374
Because of other reasons	3 (5)	2 (3)	5 (8)	
Discontinued while on combination therapy[d]	7 (12)	5 (8)	13 (22)	
Because of AE/toxicity	3 (5)	2 (3)	5 (8)	
Because of poor response	2 (3)	1 (2)	4 (7)	
Because of other reasons	2 (3)	2 (3)	4 (7)	

continued

TABLE 6 Study treatment use (*continued*)

Treatment use	Pathway			*p*-value
	A-P	D-P	P-A	
Overall				
Number (%) discontinuing treatment pathway at any time[e]	20 (19)	12 (12)	23 (21)	0.226
Because of AE/toxicity	6 (6)	4 (4)	6 (6)	0.792
Because of poor response	4 (4)	0	2 (2)	0.398
Because of other reasons	10 (10)	8 (8)	15 (14)	

a Numbers relate to patients who discontinue first-line therapy either as monotherapy or while in combination with second-line therapy. Patients who discontinue first-line monotherapy may switch to using second-line therapy only or withdraw from the treatment pathway in its entirety. Patients who discontinue first-line therapy while on combination therapy may switch to using second-line therapy only or withdraw from the pathway in its entirety.
b Numbers relate to patients who discontinue first-line therapy as monotherapy and either switch to second-line therapy only or withdraw from the pathway in its entirety.
c Numbers relate to patients who discontinue second-line therapy either as monotherapy or while in combination first-line therapy. Patients who discontinue second-line therapy while on combination may revert to first-line therapy only or withdraw from the pathway in its entirety. Patients who discontinue while on monotherapy withdraw from the pathway in its entirety.
d Numbers relate to patients who discontinue second-line therapy while in combination with first-line therapy and either revert to first-line therapy only or withdraw from the pathway in its entirety.
e Numbers relate to patients who discontinue treatment pathway prior to week 16 while on first-line therapy only, second-line therapy only or their combination.

Likewise, discontinuation overall was similar across the three arms, but more patients discontinued duloxetine because of AEs or toxicity. The proportion of patients starting second-line therapy was also similar, as were the proportions on the highest dose level at week 16. More participants discontinued or switched from duloxetine during first-line therapy and more participants discontinued intervention during the P-A pathway, but neither was statistically significant.

Numeric Rating Scale pain

None of the pairwise comparisons was statistically significant. At week 16, among participants with outcome data (i.e. complete-case analysis), mean pain in the A-P arm was 0.1 units lower (i.e. better) than in the D-P and P-A arms, but the prespecified clinically important difference of 0.5 units was either excluded from or on the edge of each pairwise CI. For D-P compared with A-P the mean difference was −0.1 (98.3% CI −0.5 to 0.3), for P-A compared with A-P the mean difference was −0.1 (98.3% CI −0.5 to 0.3) and for P-A compared with D-P the mean difference was 0.0 (98.3% CI −0.4 to 0.4) (*Table 7*). These findings were robust across a range of analyses that assessed missing data under plausible scenarios (*Figures 6* and *7*), in which the 47 (15%) instances of missing data were imputed by last observation carried forward, multiple imputation or controlled multiple imputation. In all cases, the point effects were within ± 0.1 points.

The differences at week 6 were larger among patients in the P-A arm, having greater average pain than patients in the D-P and A-P arms; however, again, none of these differences was statistically significant. For the complete-case scenario, the difference between P-A and A-P was 0.3 (98.3% CI −0.1 to 0.8; $p = 0.0492$), with similar findings in analyses of imputed data, reflecting the similar levels

TABLE 7 Response to treatment by maximum tolerated doses of monotherapies at 6 weeks and at the end of treatment pathways at 16 weeks by intention to treat

Outcome	Baseline ($N = 130$)	Week 6 (monotherapy phase) A-P ($N = 104$)	D-P ($N = 100$)	P-A ($N = 107$)	Week 16 (combination therapy phase) A-P ($N = 104$)	D-P ($N = 100$)	P-A ($N = 107$)
Average weekly pain (NRS; 0–10)							
Patients included, *n*	130	100	95	104	91	85	88
NRS pain, mean (SD)[a]	6.6 (1.5)	3.8 (2.0)	3.9 (1.9)	4.1 (2.1)	3.3 (1.8)	3.3 (1.8)	3.3 (1.8)
Change from baseline, mean (SD)		2.9 (2.0)	2.8 (2.0)	2.5 (2.2)	3.4 (2.1)	3.5 (2.1)	3.3 (2.1)
≥ 30% reduction from baseline, *n* (%)		68 (65)	63 (63)	60 (56)	68 (65)	68 (68)	68 (64)
≥ 50% reduction from baseline, *n* (%)		42 (40)	35 (35)	43 (40)	50 (48)	46 (46)	47 (44)
NRS score of ≤ 3 points, *n* (%)		38 (37)	32 (32)	36 (34)	50 (48)	43 (43)	50 (47)
Pairwise contrast, mean difference (98.3% CI); p-value							
D-P vs. A-P		0.1 (−0.3 to 0.5); 0.649			−0.1 (−0.5 to 0.3); 0.613		
P-A vs. A-P		0.3 (−0.1 to 0.8); 0.049			−0.1 (−0.5 to 0.3); 0.611		
P-A vs. D-P		0.3 (−0.2 to 0.7); 0.137			0.0 (−0.4 to 0.4); 0.996		
Combined arms							
n		299			265		
Change from baseline, mean (98.3% CI); *p*-value		2.8 (2.2 to 3.0); < 0.001			3.4 (2.9 to 3.8); < 0.001[b]		
≥ 50% reduction from baseline, *n* (%)		120 (40)			143 (54)		
NRS score of ≤ 3 points, *n* (%)		106 (35)			143 (54)		
Change in NRS from week 6 to week 16 mean (98.3% CI)							
Patients on combination therapy					1.0 (0.6 to 1.3)		
Patients on monotherapy					0.2 (−0.1 to 0.5)		
All patients					0.6 (0.3 to 0.8)		

a Measured for 7 days at baseline and for 7 days at maximum tolerated dose at weeks 6 and 16.
b $p < 0.001$ for the difference between the combined arms of monotherapy and combination treatment.

Notes
NRS score of ≤ 3 points is equivalent to mild pain achieved by 'responders'.
Data are mean (SD) or percentage (rating on a scale of 0–10) and pairwise comparisons are mean difference (98.3% CI).
For items rated on a scale of 0–10, increasing numbers indicate increasing pain.

of 'for cause' missing data in the two arms. Nevertheless, none of the arms differed on average by more than 0.4 points in any scenario and none was statistically significant at the predefined alpha = 0.0167 level. In total, there were 12 (4%) instances of missing data, meaning that the impact of missing data was small.

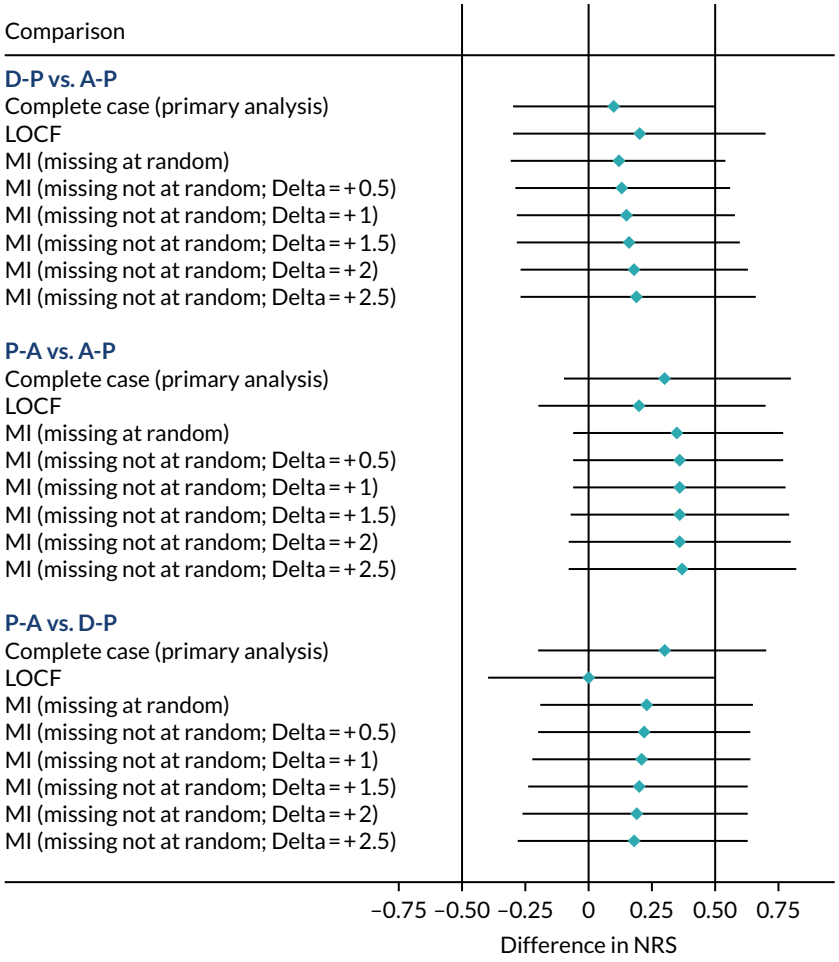

FIGURE 6 Pairwise comparisons of NRS pain score at week 6. MI, multiple imputation. LOCF, Last observation carried forward.

Response to treatment

Treatment response is summarised in *Table 8*. As noted above, duloxetine was the least well-tolerated monotherapy and had the lowest response rate (27% vs. 30% for amitriptyline and 34% for pregabalin) at week 6, although, again, this comparison was not statistically significant. The overall response rates at week 16 were 46% (A-P), 43% (D-P) and 46% (P-A).

Figure 8 shows the trajectory of average self-reported pain by randomised sequence, ranging over the 52 weeks of study (pain scores were not routinely completed for the washout periods and have not been included). Self-rated pain did not return to pre-randomisation levels in the washout periods between pathways 1 and 2 or between pathways 2 and 3. This tempers the conclusions that can be made for the change from baseline outcomes (i.e. 30% or 50% reductions), but the inclusion of period number in the statistical model meant that between-arm comparisons remained valid.

Figure 9 shows the trajectory of average NRS score by time within each pathway. The three curves largely overlap throughout the 16 weeks, suggesting that the arms have equivalent efficacy both in the monotherapy phase (i.e. weeks 0–6) and thereafter. Pain scores continued to decrease after week 6 when combination therapy was offered to participants (mean score: week 16 3.3 vs. week 6 3.9), although qualitatively the scores appeared to plateau around week 12.

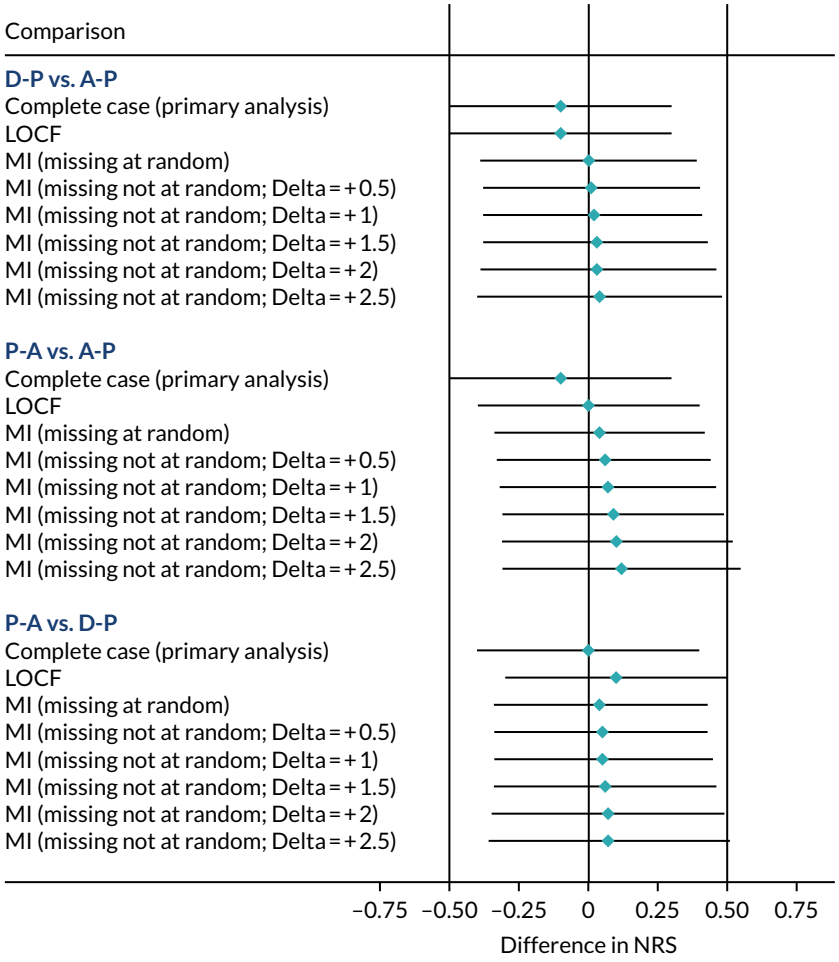

FIGURE 7 Sensitivity analysis of NRS pain score at week 16. MI, multiple imputation. LOCF, Last observation carried forward.

TABLE 8 Overview of treatment response

		Response status			
Pathway	**Number starting**	**Week 6 (monotherapy)**	***n* (%)**	**Week 16 (combination)**	***n* (%)**
A-P	104	Responders[a]	31 (30)	Responders[b]	48 (46)
		Non-responders[c]	69 (66)	Non-responders	50 (48)
		Stopped first-line therapy	21 (20)	Stopped treatment pathway for AE/poor response	11 (11)
		Started second-line therapy	17 (16)	NRS score > 3 points	41 (39)
		NRS score > 3 points	52 (50)		
		Missing	4 (4)	Missing	6 (6)
D-P	100	Responders[a]	27 (27)	Responders[b]	43 (43)
		Non-responders[c]	73 (73)	Non-responders	52 (52)
		Stopped first-line therapy	22 (22)	Stopped treatment pathway for AE/poor response	11 (11)
		Started second-line therapy	21 (21)	NRS score > 3 points	42 (42)
		NRS score > 3 points	57 (57)		
		Missing	0	Missing	5 (5)

continued

TABLE 8 Overview of treatment response (*continued*)

Pathway	Number starting	Response status			
		Week 6 (monotherapy)	*n* (%)	Week 16 (combination)	*n* (%)
P-A	107	Responders[a]	34 (32)	Responders[b]	49 (46)
		Non-responders[c]	71 (66)	Non-responders	50 (47)
		Stopped first-line therapy	19 (18)	Stopped treatment pathway for AE/poor response	13 (12)
		Started second-line therapy	16 (15)	NRS score > 3 points	38 (36)
		NRS score > 3 points	55 (51)		
		Missing	2 (2)	Missing	8 (7)
Complete case: 7-day average pain, mean (SD) [n]					
A-P		3.8 (2.0) [100]		3.3 (1.8) [91]	
D-P		3.9 (1.9) [95]		3.3 (1.8) [85]	
P-A		4.1 (2.1) [104]		3.3 (1.8) [88]	

a Remained on monotherapy with a NRS score of ≤ 3 points at the week 6 visit.
b NRS score of ≤ 3 points at the week 16 visit without discontinuation of intervention for AE or poor response.
c More than one criteria may apply.

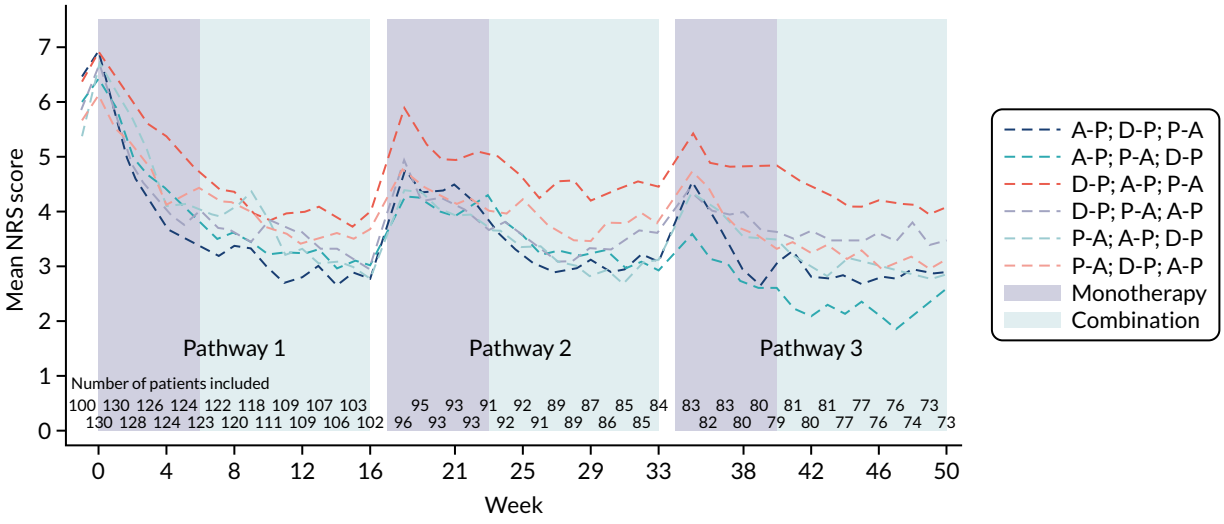

FIGURE 8 Self-reported NRS pain by time in study.

Figure 10 shows the same data as the previous figure, but separately for patients remaining on monotherapy or starting combination therapy on or after week 6. By definition, patients starting combination therapy had higher NRS scores (i.e. worse pain control) at week 6, with average pain levels appearing to plateau in the weeks prior to this. Thereafter, the curves began to converge, with a further mean drop of 1 NRS point among patients on combination therapy (again plateauing over the last weeks of the pathway) compared with 0.2 points among patients on monotherapy (*Table 9*). This suggests a benefit of combination therapy among patients who had less response to monotherapy alone.

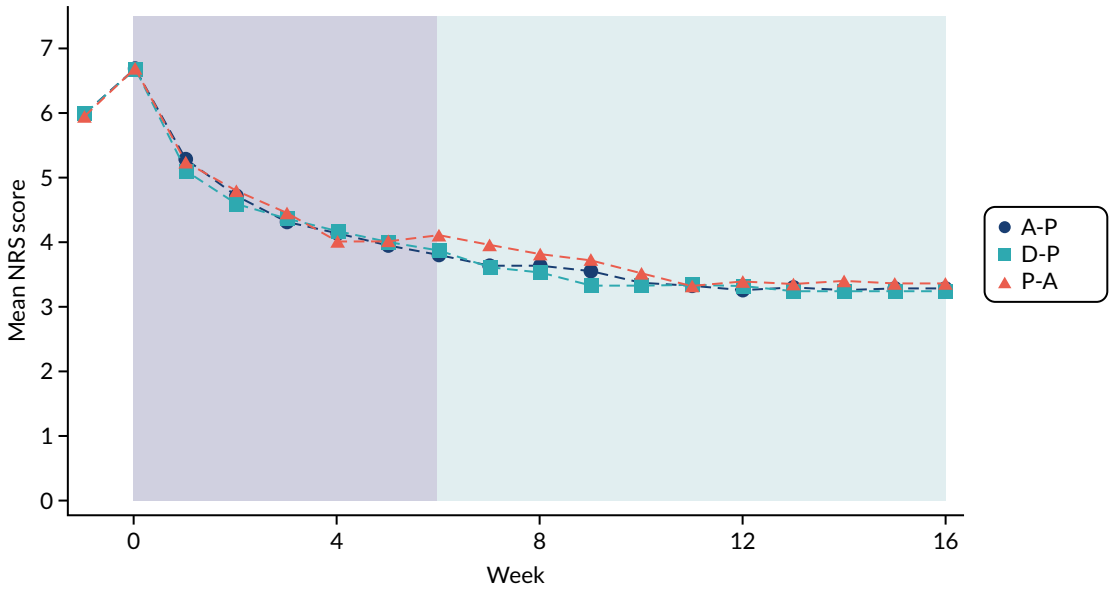

FIGURE 9 Self-reported NRS pain by treatment pathway.

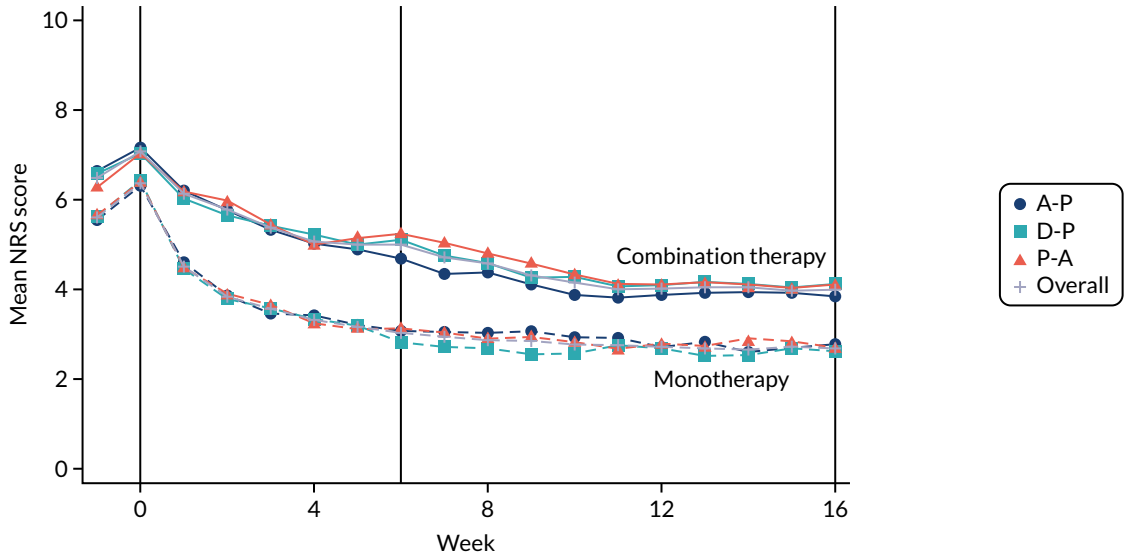

FIGURE 10 Self-reported NRS pain by use of combination therapy and treatment pathway.

TABLE 9 Change from week 6 to week 16 by treatment pathway and use of combination therapy

	Treatment pathway			
Outcome	**A-P**	**D-P**	**P-A**	**All arms**
Started combination therapy	0.9 (0.4 to 1.4)	0.9 (0.4 to 1.5)	1.1 (0.5 to 1.6)	1.0 (0.6 to 1.3)
Remained on monotherapy	0.1 (−0.4 to 0.6)	0.2 (−0.3 to 0.7)	0.3 (−0.2 to 0.8)	0.2 (−0.1 to 0.5)
Overall change by arm	0.5 (0.1 to 0.8)	0.5 (0.2 to 0.9)	0.7 (0.3 to 1.0)	0.6 (0.3 to 0.8)

Figures are mean (98.3% CI) change from week 6 to week 16.

Subgroup analyses

Further exploratory work looked at whether or not there were subgroups of patients who responded better to some therapies. *Figure 11* depicts patient response to monotherapy at week 6 via a Venn diagram. Although most patients responded either to none ($n = 37$) or all ($n = 13$) of the therapies, 30 of the 80 patients who provided data had different responses to the treatments.

The results of the subgroup analyses are presented in *Appendix 4*, *Figure 16*. Pain was, on average, higher among younger (< 60 years) patients than among the older (≥ 60 years) patients, but the three pathways showed similar efficacy within each of the two subgroups (see *Figure 16a*). A similar theme was apparent for baseline pain score, with week 16 pain being higher among patients with more severe pain (i.e. a NRS score of ≥ 7 points) but no interaction with treatment (see *Figure 16b*).

The average week 16 NRS scores were similar across the three pain phenotypes (see *Figure 16c*). There were, however, some interactions among the individual NPSI components, with a suggestion that D-P was less suited to participants with higher NPSI scores.

There was some evidence of an interaction between treatment and baseline mood. The A-P pathway was notably worse at 16 weeks for patients with high levels of anxiety or depression. Patients with moderate anxiety or depression (scores below 15) had similar responses regardless of treatment arm (see *Figure 16j* and *k*).

Pain was also investigated in relation to whether or not the patient had previously used the three study drugs (i.e. amitriptyline, duloxetine and pregabalin) or any opioids (see *Figure 16l–o*). For all four drug options, patients who had previously been prescribed drugs reported higher pain scores than patients who had not, most notably opioids. Nevertheless, the difference between treatment arms appeared unaffected by previous medication use.

Finally, pain responses during the period of the UK lockdown due to COVID-19 (defined as on/after 20 March 2020) were similar to those measured prior to lockdown, meaning that the treatment comparisons were similar both within lockdown and outside lockdown (see *Figure 16p* and *q*). There was no apparent change in weekly NRS scores following imposition of lockdown measures, or any other temporal changes.

Tolerability

Tolerability (rated on a 0–10 NRS, with 10 being least tolerable) was similar between arms at weeks 6 and 16. Scores at weeks 6 and 16 were also similar, suggesting no perceived worsening in side effects with the introduction of combination therapy. In fact, self-reported tolerability was slightly better at week 16 than in week 6, albeit not statistically significantly so (*Table 10*).

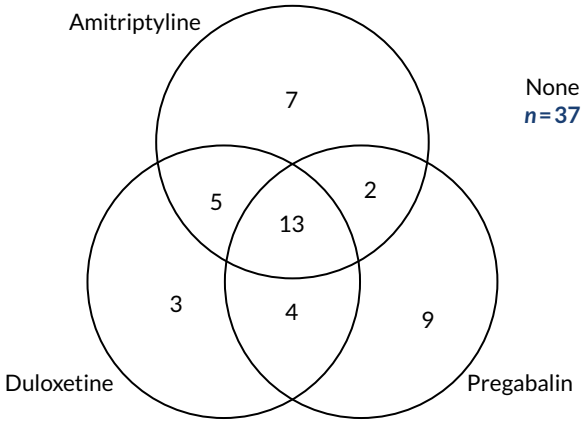

FIGURE 11 Response to monotherapy among patients starting all three pathways. Response defined as a NRS score of ≤ 3 points and no informative treatment withdrawal. Four patients provided no data to at least one pathway.

TABLE 10 Patient-reported tolerability

Tolerability[a]	Week 6			Week 16		
	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)
Responses, *n*	92	86	96	83	84	83
Discontinued because of adverse effect or poor response, *n* (%)	6 (6)	2 (2)	6 (6)	10 (10)	4 (4)	8 (8)
Tolerability of unwanted side effects over past 7 days, mean (SD)	2.2 (2.5)	2.1 (2.3)	2.4 (2.9)	2.3 (2.5)	2.1 (2.6)	1.9 (2.5)

a Range 0–10. Higher scores indicate less tolerability.

Quality of life

General health (assessed by SF-36), health utility (assessed by EQ-5D-5L) and anxiety/depression (assessed by HADS) are shown in *Table 11*. Self-reported QoL was similar across the three arms and no consistent patterns were observed among the QoL inventories. Some of the comparisons were statistically significant. After 6 weeks of treatment, duloxetine was associated with worse limitations due to physical health compared with amitriptyline and pregabalin, but was preferable with regard to general health, as assessed via SF-36 (*Figure 12*) and EQ-5D-5L. All differences were modest in clinical or psychometric terms. No statistically or clinically significant differences were found at 16 weeks.

TABLE 11 Quality of life, health utility and anxiety/depression

Outcome	Week 6			Week 16		
	A-P	D-P	P-A	A-P	D-P	P-A
Starting pathway, *n*	104	100	107	104	100	107
EQ-5D (higher scores indicate better health state) *EQ-5D-5L (crosswalk)*						
n	93	87	99	86	86	86
Mean (SD)	0.516 (0.266)	0.540 (0.237)	0.489 (0.251)	0.509 (0.253)	0.511 (0.276)	0.537 (0.243)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	0.029 (−0.023 to 0.081); 0.187			−0.006 (−0.057 to 0.044); 0.766		
P-A vs. A-P	−0.031 (−0.082 to 0.020); 0.149			0.009 (−0.041 to 0.059); 0.673		
P-A vs. D-P	−0.060 (−0.111 to −0.008); 0.005			0.015 (−0.035 to 0.065); 0.468		
EQ-5D (thermometer)						
n	92	87	99	86	85	86
Mean (SD)	56.5 (22.1)	55.4 (20.4)	56.3 (21.7)	55.7 (22.4)	57.3 (22.4)	57.7 (22.4)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	−0.4 (−5.2 to 4.4); 0.847			2.2 (−3.1 to 7.5); 0.316		
P-A vs. A-P	−0.8 (−5.5 to 3.9); 0.673			1.6 (−3.6 to 6.9); 0.451		
P-A vs. D-P	−0.4 (−5.2 to 4.3); 0.821			−0.6 (−5.8 to 4.7); 0.793		

continued

TABLE 11 Quality of life, health utility and anxiety/depression (*continued*)

Outcome	Week 6			Week 16		
	A-P	D-P	P-A	A-P	D-P	P-A
SF-36 (higher scores indicate better QoL)						
Physical health component						
n	93	87	99	86	86	86
Mean (SD)	25.4 (12.5)	22.6 (12.6)	24.5 (13.3)	23.6 (13.0)	24.1 (13.8)	24.1 (13.1)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	−2.9 (−4.9 to −0.9); < 0.001			0.4 (−1.9 to 2.7); 0.711		
P-A vs. A-P	−1.4 (−3.4 to 0.5); 0.078			−0.4 (−2.6 to 1.9); 0.699		
P-A vs. D-P	1.5 (−0.5 to 3.4); 0.067			−0.7 (−3.0 to 1.5); 0.444		
Mental health component						
n	93	87	99	86	86	86
Mean (SD)	46.7 (13.0)	47.8 (11.8)	47.6 (12.2)	46.6 (12.8)	46.3 (11.0)	47.4 (12.3)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	1.3 (−1.0 to 3.6); 0.182			−0.2 (−2.5 to 2.2); 0.855		
P-A vs. A-P	1.1 (−1.1 to 3.4); 0.229			0.8 (−1.5 to 3.1); 0.417		
P-A vs. D-P	−0.1 (−2.4 to 2.1); 0.875			1.0 (−1.4 to 3.3); 0.317		
HADS (higher scores indicate greater symptoms)						
Anxiety						
n	93	85	99	86	86	86
Mean (SD)	7.5 (5.1)	7.4 (4.6)	6.7 (4.4)	7.7 (5.4)	7.3 (4.8)	7.0 (4.6)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	−0.1 (−0.9 to 0.7); 0.826			−0.3 (−1.2 to 0.6); 0.449		
P-A vs. A-P	−0.5 (−1.3 to 0.3); 0.138			−0.4 (−1.4 to 0.5); 0.253		
P-A vs. D-P	−0.4 (−1.2 to 0.4); 0.213			−0.1 (−1.1 to 0.8); 0.705		
Depression						
n	93	85	99	86	86	86
Mean (SD)	7.4 (4.7)	7.3 (4.4)	7.0 (4.5)	7.3 (4.9)	7.5 (4.5)	7.2 (4.5)
Pairwise comparisons, mean difference (98.3% CI); *p*-value						
D-P vs. A-P	−0.2 (−1.0 to 0.6); 0.489			−0.1 (−0.9 to 0.6); 0.698		
P-A vs. A-P	−0.4 (−1.1 to 0.4); 0.274			−0.0 (−0.8 to 0.7); 0.903		
P-A vs. D-P	−0.1 (−0.9 to 0.7); 0.705			0.1 (−0.6 to 0.8); 0.786		

Other pain inventories and insomnia

As with the NRS, the NPSI and BPI-MSF were largely similar across arms at 6 and 16 weeks (*Table 12*). In general, the D-P arm had the highest pain scores at week 16, with the P-A arm having the lowest, but none of the comparisons was statistically significant. By contrast, week 6 pain scores tended to be higher in the P-A arm, with two BPI-MSF scores (worst pain over 24 hours and overall pain severity) being significantly lower in the A-P treatment pathway.

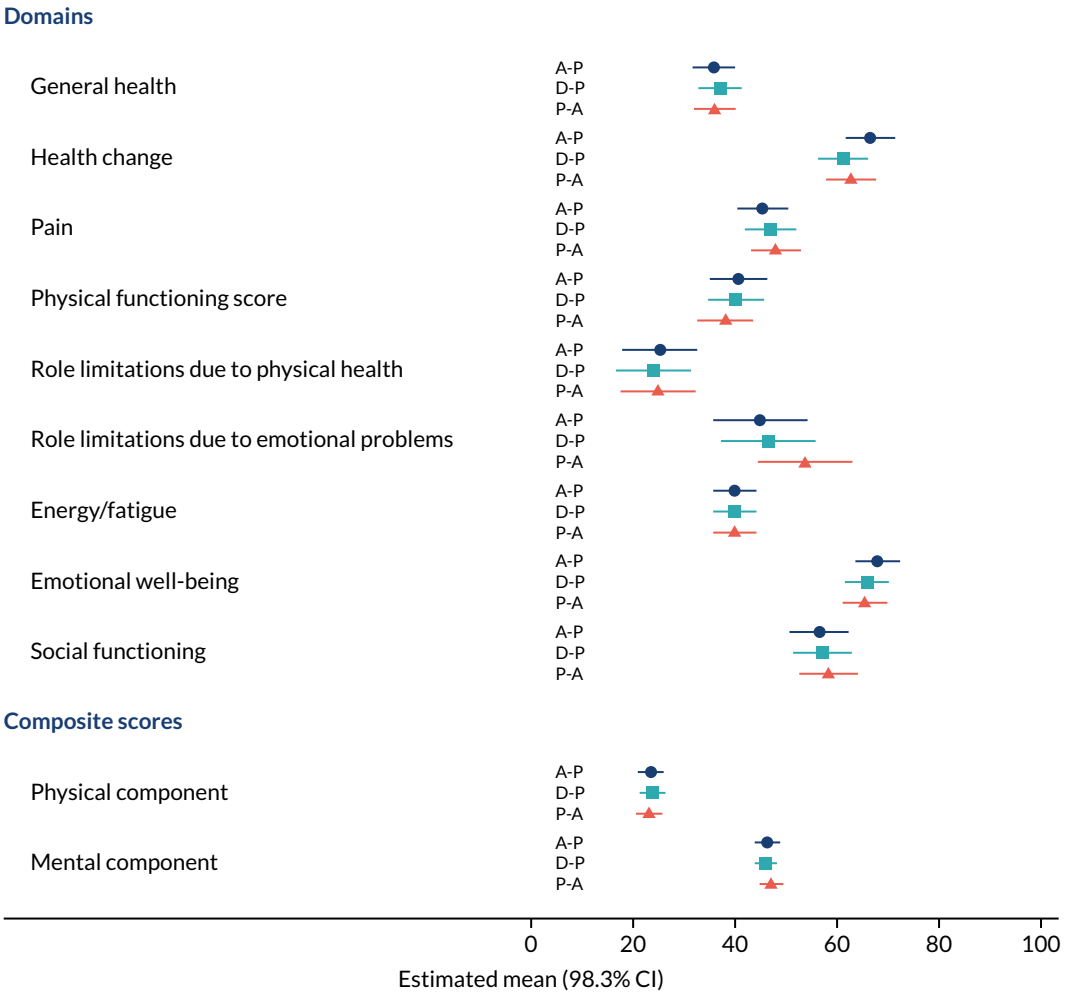

FIGURE 12 Short Form questionnaire-36 items domains. Graphs depict the model-based mean and CI for each treatment arm for each of the nine domains at week 16. Higher scores indicate better QoL.

TABLE 12 Neuropathic Pain Symptom Inventory and BPI-MSF

Outcome	Baseline (*N* = 130)	Monotherapy phase (week 6)			Combination treatment phase (week 16)		
		A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)
Patients included, *n*	130	93	87	99	86	86	86
NPSI individual components (range 0–10; higher is greater pain), mean (SD)							
Superficial spontaneous burning pain	6.0 (2.9)	3.4 (2.9)	3.6 (2.7)	3.9 (3.0)	3.2 (3.0)	3.7 (2.8)	3.4 (2.8)
Deep spontaneous pressing pain	4.8 (2.8)	3.0 (2.7)	2.9 (2.4)	3.3 (2.9)	2.9 (2.8)	3.4 (2.5)	3.1 (2.8)
Paroxysmal pain	5.5 (2.9)	3.5 (2.9)	3.4 (2.5)	3.6 (2.8)	3.3 (3.0)	3.8 (2.9)	3.6 (2.8)
Evoked pain	4.3 (2.6)	2.9 (2.5)	2.7 (2.3)	2.9 (2.3)	3.2 (2.7)	3.0 (2.5)	3.0 (2.6)
Paraesthesia/ dysaesthesia	6.3 (2.7)	4.2 (2.7)	4.3 (2.7)	4.3 (2.8)	4.1 (3.0)	4.0 (2.9)	4.4 (2.9)
Total score (range 0–50)	52.4 (19.5)	33.7 (21.9)	33.2 (20.1)	34.6 (20.9)	33.8 (24.4)	35.0 (21.5)	33.9 (21.9)

continued

TABLE 12 Neuropathic Pain Symptom Inventory and BPI-MSF (*continued*)

Outcome	Baseline (*N* = 130)	Monotherapy phase (week 6)			Combination treatment phase (week 16)		
		A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)
BPI-MSF (range 0–10; higher is greater pain), mean (SD)							
Pain severity score	6.1 (1.7)	3.8 (2.0)[a]	3.9 (1.7)	4.3 (2.2)	3.7 (2.0)	3.8 (1.9)	3.5 (2.0)
Pain interference score	5.9 (2.4)	4.0 (2.6)	4.2 (2.5)	4.3 (2.7)	4.1 (2.7)	4.0 (2.6)	3.7 (2.5)
Worst pain in last 24 hours	7.2 (1.8)	4.3 (2.2)[b]	4.5 (2.0)	5.0 (2.5)	4.4 (2.3)	4.5 (2.3)	4.3 (2.5)
Least pain in last 24 hours	5.0 (2.2)	3.1 (2.2)	3.2 (1.9)	3.5 (2.4)	3.0 (2.2)	3.0 (2.0)	2.8 (2.0)
Average pain	6.1 (1.7)	4.0 (1.9)	4.1 (1.6)	4.4 (2.2)	3.8 (2.0)	3.9 (1.9)	3.7 (2.0)
Pain right now	6.0 (2.2)	3.5 (2.3)	3.7 (2.1)	4.1 (2.6)	3.5 (2.4)	3.6 (2.3)	3.2 (2.3)

a Patients in the A-P arm reported lower pain than patients in the P-A arm (mean difference 0.5, 98.3% CI 0.0 to 1.0; $p = 0.012$).
b Patients in the A-P arm reported lower pain than patients in the P-A arm (mean difference 0.7, 98.3% CI 0.1 to 1.3; $p = 0.005$).

Self-reported insomnia (via the ISI) is summarised in *Table 13*. Patients rated their insomnia worse in the D-P arm than in the A-P arm, both at week 6 (mean difference = 1.5, 98.3% CI 0.0 to 3.1; $p = 0.016$) and at week 16 (mean difference = 1.5, 98.3% CI 0.1 to 3.0; $p = 0.010$).

Patient impression of change and treatment preference

Finally, participants were asked to complete a global impression of change (using the PGIC) at the end of each pathway and their preferred treatment if they had completed the three pathways (*Table 14*). The treatments were rated positively among this group, with 44%, 43% and 49% of patients reporting 'much improved' or 'very much improved' for A-P, D-P and P-A, respectively (Kruskal–Wallis test $p = 0.70$).

TABLE 13 Insomnia Severity Index

Outcome	Baseline (*N* = 130)	Monotherapy phase (week 6)			Combination treatment phase (week 16)		
		A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)
Patients included, *n*	130	93	87	99	86	86	86
ISI total score (0–28; higher scores indicate greater insomnia), mean (SD)	18.1 (5.9)	11.8 (7.3)[a]	13.8 (6.3)	12.1 (7.1)	11.4 (7.3)[a]	13.3 (6.8)	12.1 (6.4)

a Patients in the A-P arm reported lower insomnia scores than patients in the P-A arm at week 6 (mean difference 1.5, 98.3% CI 0.0 to 3.1; $p = 0.016$) and at week 16 (mean difference 1.5, 98.3% CI 0.1 to 3.0; $p = 0.010$).

TABLE 14 Patient impression of change and treatment preference

Outcome	Treatment pathway		
	A-P	D-P	P-A
Starting pathway, *n*	104	100	107
PGIC, *n* (%)			
Very much improved	11 (11)	8 (8)	12 (12)
Much improved	32 (33)	33 (35)	36 (37)
Minimally improved	25 (26)	26 (27)	22 (23)
No change	19 (20)	17 (18)	16 (16)
Minimally worse	6 (6)	8 (8)	10 (10)
Much worse	4 (4)	3 (3)	1 (1)
Kruskal–Wallis test for difference between groups	$p = 0.702$		
Preferred treatment, *n* (%)			
Stated preference at end of study[a]	11 (24)	15 (33)	20 (43)
Chi-squared test for difference between groups:	$p = 0.266$		

a Excludes participants who expressed equal preference for two different pathways: one patient stated D-P and P-A and one patient stated D-P and A-P.

On reaching the end of the study, participants were asked to rate their preferred treatment of the study. The most popular choice was P-A (43%), followed by D-P (33%) and A-P (24%), although this comparison was not statistically significant ($p = 0.266$).

Adverse events

Adverse events are summarised by pathway in *Table 15*. Fatigue was the most commonly reported AE and was similarly prevalent in each pathway. The most notable difference was in the incidence of dry mouth, which was associated with amitriptyline (A-P, 32%; P-A, 17%; D-P, 8%) ($p < 0.001$). Dizziness was more common in patients in the P-A arm (24%) than in patients in the A-P (12%) and D-P (16%) arms, and nausea was highest (23%) in the D-P arm (vs. 5% in the A-P arm and 7% in the P-A arm; $p = 0.001$).

TABLE 15 AEs by pathway

AE category	A-P ($N = 104$)		D-P ($N = 100$)		P-A ($N = 107$)		*p*-value
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	
Fatigue	25	21 (20)	23	18 (18)	25	22 (21)	0.880
Dizziness	12	12 (12)	17	16 (16)	33	26 (24)	0.036
Dry mouth	34	33 (32)	8	8 (8)	20	18 (17)	< 0.001
Sedation	22	21 (20)	14	11 (11)	18	15 (14)	0.167
Diarrhoea	22	18 (17)	17	16 (16)	11	9 (8)	0.122

continued

TABLE 15 AEs by pathway (*continued*)

AE category	A-P (*N* = 104)		D-P (*N* = 100)		P-A (*N* = 107)		*p*-value
	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	
Fall	12	7 (7)	17	12 (12)	17	10 (9)	0.880
Oedema	10	9 (9)	13	10 (10)	18	17 (16)	0.150
Nausea	5	5 (5)	27	23 (23)	8	7 (7)	0.001
Constipation	13	11 (11)	15	13 (13)	9	8 (7)	0.469
Headaches	11	9 (9)	16	14 (14)	10	8 (7)	0.335
Vomiting	8	7 (7)	12	11 (11)	8	8 (7)	0.513
Excessive sweating	11	9 (9)	10	10 (10)	6	6 (6)	0.576
Insomnia	8	6 (6)	9	8 (8)	7	7 (7)	0.902
Abdominal cramping	6	5 (5)	8	6 (6)	4	4 (4)	0.580
Ataxia	6	4 (4)	4	4 (4)	8	8 (7)	0.415
Pruritus	2	2 (2)	9	8 (8)	5	5 (5)	0.170
Weight gain	3	3 (3)	1	1 (1)	10	10 (9)	NC
Decreased appetite	5	5 (5)	5	5 (5)	2	2 (2)	0.401
Inability to concentrate	5	5 (5)	1	1 (1)	6	6 (6)	0.242
Cardiac ischaemia	3	2 (2)	3	3 (3)	5	5 (5)	NC
Hypoglycaemia	4	4 (4)	3	3 (3)	4	4 (4)	NC
Blurred vision	2	2 (2)	1	1 (1)	5	5 (5)	NC
Low mood	6	6 (6)	1	1 (1)	1	1 (1)	0.112
Hypotension	1	1 (1)	5	5 (5)	1	1 (1)	NC
Restless legs	2	2 (2)	5	5 (5)	0		NC
Anxiety	2	2 (2)	2	1 (1)	2	2 (2)	NC
Hyperglycaemia	3	2 (2)	1	1 (1)	2	2 (2)	NC
Dysarthria	1	1 (1)	0		4	4 (4)	NC
Kidney dysfunction	1	1 (1)	2	2 (2)	2	2 (2)	NC
Hallucinations	3	1 (1)	0		1	1 (1)	NC
Heart failure	0		2	2 (2)	1	1 (1)	NC
Liver dysfunction	1	1 (1)	1	1 (1)	1	1 (1)	NC
Tachycardia	2	1 (1)	1	1 (1)	0		NC
Transient ischaemic attack	0		3	3 (3)	0		NC
Increased appetite	2	1 (1)	0		0		NC
Urinary retention	1	1 (1)	1	1 (1)	0		NC
Seizure	0		1	1 (1)	0		NC
Other	180	72 (69)	181	70 (70)	190	77 (72)	

NC, not calculable.

Table 16 shows AEs further split by the time they occurred (i.e. before or after 6 weeks) and SAEs are tabulated in *Table 17*. One SUSAR occurred [one participant experienced an atrioventricular heart block (Mobitz II) in the P-A arm 11 weeks into the first treatment pathway and while on amitriptyline, having switched from pregabalin at the week 6 visit].

TABLE 16 Adverse events with a frequency of ≥ 5% in any arm by treatment phase

	A-P (*N* = 104)			D-P (*N* = 100)			P-A (*N* = 107)		
		Patients, *n* (%)			Patients, *n* (%)			Patients, *n* (%)	
AE category	Events, *n*	Started < 6 weeks	Started > 6 weeks	Events, *n*	Started < 6 weeks	Started > 6 weeks	Events, *n*	Started < 6 weeks	Started > 6 weeks
Number in study		104	96		100	94		107	103
Fatigue	25	18 (17)	5 (5)	23	17 (17)	4 (4)	25	11 (10)	13 (13)
Dizziness	12	8 (8)	6 (6)	17	8 (8)	8 (9)	33	19 (18)	11 (11)
Dry mouth	34	22 (21)	12 (13)	8	5 (5)	3 (3)	20	10 (9)	10 (10)
Sedation	22	19 (18)	2 (2)	14	6 (6)	6 (6)	18	10 (9)	7 (7)
Diarrhoea	22	8 (8)	11 (11)	17	10 (10)	7 (7)	11	6 (6)	4 (4)
Fall	12	3 (3)	5 (5)	17	6 (6)	7 (7)	17	5 (5)	7 (7)
Oedema	10	2 (2)	7 (7)	13	5 (5)	7 (7)	18	14 (13)	3 (3)
Nausea	5	4 (4)	1 (1)	27	19 (19)	6 (6)	8	6 (6)	2 (2)
Constipation	13	9 (9)	4 (4)	15	8 (8)	6 (6)	9	5 (5)	3 (3)
Headaches	11	8 (8)	1 (1)	16	10 (10)	7 (7)	10	7 (7)	2 (2)
Vomiting	8	5 (5)	2 (2)	12	9 (9)	3 (3)	8	1 (1)	7 (7)
Excessive sweating	11	7 (7)	4 (4)	10	7 (7)	3 (3)	6	1 (1)	5 (5)
Insomnia	8	3 (3)	3 (3)	9	7 (7)	2 (2)	7	3 (3)	6 (6)
Abdominal cramping	6	4 (4)	2 (2)	8	4 (4)	2 (2)	4	3 (3)	1 (1)
Ataxia	6	1 (1)	3 (3)	4	2 (2)	2 (2)	8	7 (7)	1 (1)
Pruritus	2	1 (1)	1 (1)	9	5 (5)	3 (3)	5	3 (3)	2 (2)
Weight gain	3	2 (2)	1 (1)	1	1 (1)	0	10	7 (7)	3 (3)
Decreased appetite	5	4 (4)	1 (1)	5	5 (5)	0	2	0	2 (2)
Inability to concentrate	5	4 (4)	1 (1)	1	1 (1)	0	6	6 (6)	0
Low mood	6	5 (5)	1 (1)	1	1 (1)	0	1	1 (1)	0
Hypotension	1	0	1 (1)	5	0	5 (5)	1	1 (1)	0
Restless legs	2	1 (1)	1 (1)	5	1 (1)	4 (4)	0	0	0

AEs shown have an incidence of at least 5% in any group. Participants may contribute to both < 6 weeks and > 6 weeks if the same AE occurred in both phases.

TABLE 17 Serious adverse events

	A-P (*N* = 104)		D-P (*N* = 100)		P-A (*N* = 107)	
SAE category	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Any SAE	6	4 (4)	12	10 (10)	13	10 (9)
Vomiting	1	1 (1)	1	1 (1)	1	1 (1)
Cardiac ischaemia	0		0		2	2 (2)
Dizziness	0		0		2	2 (2)
Headaches	0		2	1 (1)	0	
Hyperglycaemia	2	1 (1)	0		0	
Hypoglycaemia	0		1	1 (1)	1	1 (1)
Kidney dysfunction	0		0		1	1 (1)
Transient ischaemic attack	0		1	1 (1)	0	
Other	3	3 (3)	7	7 (7)	6	6 (6)

The remaining tables (*Tables 18–20*) focus on AEs of moderate or severe intensity that are related to one or both study medications. In total, 97 such events occurred, affecting 19% of patients in the A-P arm, 22% of patients in the D-P arm and 21% of patients in the P-A arm ($p = 0.719$) (see *Table 18*). A post hoc analysis looked at days affected by moderate or severe related AEs (see *Table 19*) while in study follow-up, which for the majority of patients was zero but for the groups as a whole resulted in 84, 69 and 73 days per 1000 days of follow-up in the A-P, D-P and P-A arms, respectively ($p = 0.858$). Most events started during monotherapy but continued to affect patients beyond week 6, by which point combination therapy may have started. The mean days affected for each category is displayed visually in *Figure 13* and in *Table 20*. The AEs with the longest average person-day impacts were dry mouth in the A-P arm (191 days/1000 days of follow-up) and fatigue in all arms (109 days/1000 days of follow-up).

TABLE 18 Moderate or severe AEs by category

	A-P (*N* = 104)		D-P (*N* = 100)		P-A (*N* = 107)	
AE category	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)
Any moderate or severe probably related AE[a]	30	20 (19)	35	22 (22)	32	22 (21)
Fatigue	11	10 (10)	7	7 (7)	9	9 (8)
Fall	7	6 (6)	9	5 (5)	9	6 (6)
Dizziness	4	4 (4)	6	6 (6)	12	12 (11)
Sedation	7	7 (7)	4	4 (4)	7	6 (6)
Oedema	5	5 (5)	6	6 (6)	6	6 (6)

TABLE 18 Moderate or severe AEs by category (*continued*)

	A-P (*N* = 104)		D-P (*N* = 100)		P-A (*N* = 107)	
AE category	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**	**Events, *n***	**Patients, *n* (%)**
Vomiting	3	3 (3)	7	7 (7)	5	5 (5)
Diarrhoea	5	5 (5)	7	7 (7)	2	2 (2)
Insomnia	3	3 (3)	6	6 (6)	3	3 (3)
Headaches	2	2 (2)	8	7 (7)	1	1 (1)
Nausea	1	1 (1)	9	8 (8)	1	1 (1)
Dry mouth	8	8 (8)	0		2	2 (2)
Abdominal cramping	4	3 (3)	4	4 (4)	1	1 (1)
Ataxia	4	3 (3)	2	2 (2)	2	2 (2)
Cardiac ischaemia	1	1 (1)	2	2 (2)	5	5 (5)
Excessive sweating	4	4 (4)	4	4 (4)	0	
Inability to concentrate	3	3 (3)	1	1 (1)	3	3 (3)
Constipation	3	3 (3)	3	3 (3)	0	
Low mood	5	5 (5)	0		1	1 (1)
Blurred vision	1	1 (1)	1	1 (1)	3	3 (3)
Hypotension	0		4	4 (4)	1	1 (1)
Pruritus	1	1 (1)	2	2 (2)	2	2 (2)
Hypoglycaemia	2	2 (2)	1	1 (1)	1	1 (1)
Kidney dysfunction	1	1 (1)	1	1 (1)	2	2 (2)
Anxiety	1	1 (1)	1	1 (1)	1	1 (1)
Decreased appetite	0		2	2 (2)	1	1 (1)
Liver dysfunction	1	1 (1)	1	1 (1)	1	1 (1)
Transient ischaemic attack	0		3	3 (3)	0	
Dysarthria	1	1 (1)	0		1	1 (1)
Heart failure	0		1	1 (1)	1	1 (1)
Hyperglycaemia	2	1 (1)	0		0	
Restless legs	1	1 (1)	1	1 (1)	0	
Hallucinations	0		0		1	1 (1)
Seizure	0		1	1 (1)	0	
Urinary retention	1	1 (1)	0		0	
Weight gain	0		0		1	1 (1)

a $p = 0.719$.

TABLE 19 Moderate or severe treatment-related AEs

	Treatment pathway			
	A-P (*N* = 104)	D-P (*N* = 100)	P-A (*N* = 107)	*p*-value
Total duration				
Number of patients with AE/number of patients in follow-up	20/104	22/100	22/107	
Average weeks affected per person	1.2	1.0	1.1	0.858
Days affected per 1000 days of follow-up	84.0	68.7	72.6	
Pairwise comparisons, IRR (98.3% CI)				
D-P vs. A-P	0.70 (0.15 to 3.32)			0.582
P-A vs. A-P	0.81 (0.18 to 3.75)			0.747
P-A vs. D-P	1.17 (0.25 to 5.53)			0.814
First-line monotherapy: weeks 1–6				
Number of patients with AE/number of patients in follow-up	14/104	11/100	11/107	
Average weeks affected per person	0.4	0.4	0.2	0.742
Days affected per 1000 days of follow-up	74.6	73.8	37.4	
Pairwise comparisons, IRR (98.3% CI)				
D-P vs. A-P	0.97 (0.12 to 7.62)			0.971
P-A vs. A-P	0.55 (0.07 to 4.41)			0.493
P-A vs. D-P	0.57 (0.07 to 4.51)			0.514
Combination therapy				
Number of patients with AE/number of patients in follow-up	8/45	13/42	10/47	
Average weeks affected per person	1.1	0.9	0.9	0.881
Days affected per 1000 days of follow-up	283.2	206.1	244.0	
Pairwise comparisons IRR (98.3% CI)				
D-P vs. A-P	0.75 (0.08 to 6.86)			0.758
P-A vs. A-P	1.19 (0.14 to 10.10)			0.846
P-A vs. D-P	1.58 (0.18 to 14.07)			0.617
Monotherapy vs. combination therapy				
Number of days affected/total follow-up				
Monotherapy	731/11,998			
Combination therapy	894/8480			
Days affected per 1000 days of follow-up				
Monotherapy	60.9			
Combination therapy	105.4			
Combination vs. monotherapy, IRR (98.3% CI)	1.72 (0.45 to 6.56)			0.331

IRR, incidence rate ratio.

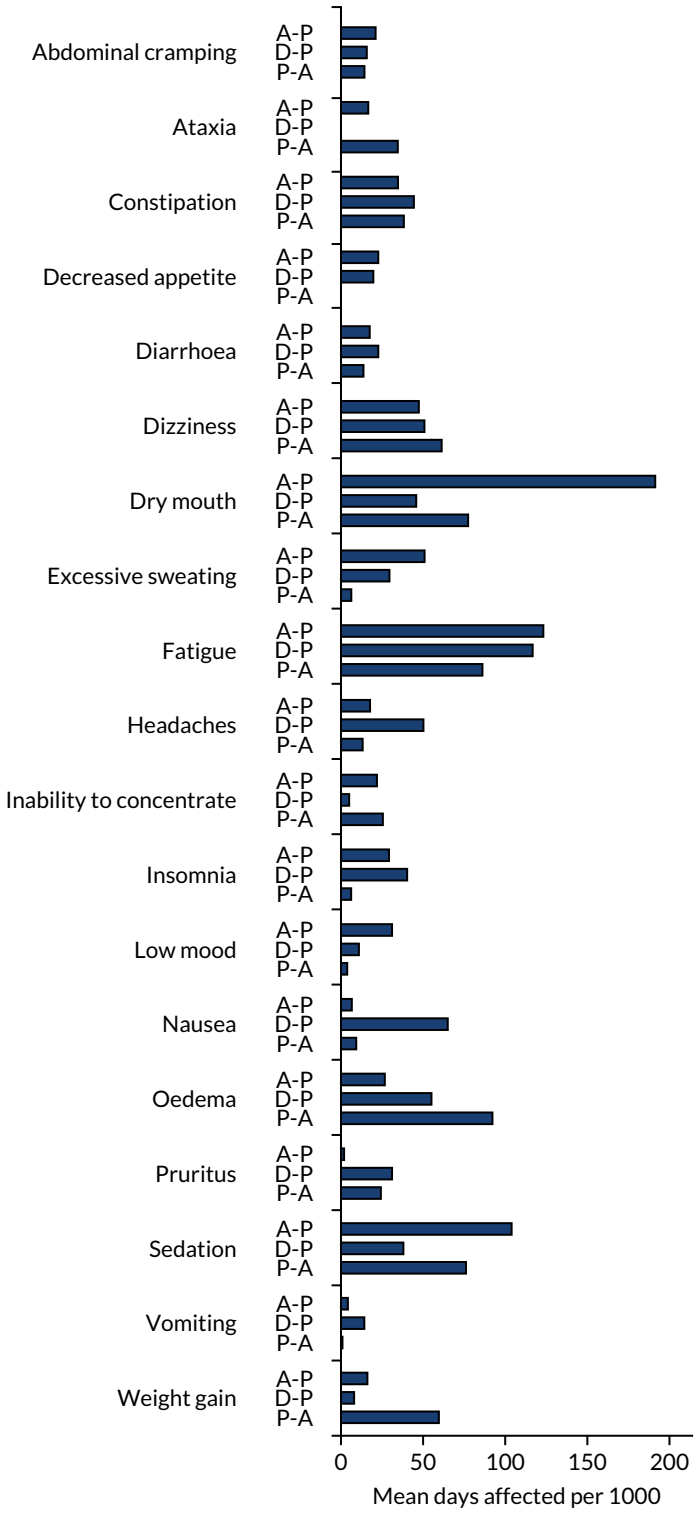

FIGURE 13 Days impacted by adverse effects.

TABLE 20 Days affected by adverse effects

Days affected by adverse effects	A-P			D-P			P-A		
	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16
Patients, *n*	104	104	96	100	100	94	107	107	103
Total person-weeks	1503.6	598.4	899.1	1483.7	582.1	897.6	1582.0	636.9	943.4
Abdominal cramping									
Average weeks affected per person	2.1	0.6	1.7	1.6	0.5	1.1	1.5	0.6	0.9
Days affected per 1000 days of follow-up	21.1	14.3	25.7	15.7	13.4	17.3	14.3	14.1	14.4
Ataxia									
Average weeks affected per person	1.7	0.4	1.4	0.0	0.0	0.0	3.6	1.4	2.3
Days affected per 1000 days of follow-up	16.6	10.0	21.1	0.1	0.1	0.1	34.6	32.5	36.1
Constipation									
Average weeks affected per person	3.5	1.2	2.5	4.6	1.9	2.8	4.0	0.9	3.1
Days affected per 1000 days of follow-up	34.7	29.1	38.6	44.4	47.1	42.8	38.3	22.5	49.0
Decreased appetite									
Average weeks affected per person	2.3	0.9	1.4	2.0	1.0	1.1	0.0	0.0	0.0
Days affected per 1000 days of follow-up	22.7	23.5	22.2	19.7	23.8	17.2	0.0	0.0	0.0
Diarrhoea									
Average weeks affected per person	1.8	0.6	1.3	2.4	0.8	1.6	1.4	1.0	0.5
Days affected per 1000 days of follow-up	17.5	14.4	19.7	22.7	19.4	24.9	13.7	23.3	7.3
Dizziness									
Average weeks affected per person	4.8	1.2	3.8	5.3	1.1	4.4	6.3	2.9	3.6
Days affected per 1000 days of follow-up	47.4	30.8	58.7	50.8	26.0	67.2	61.3	68.5	56.5
Dry mouth									
Average weeks affected per person	19.4	5.5	14.7	4.8	1.2	3.7	8.0	1.7	6.4
Days affected per 1000 days of follow-up	191.3	137.4	228.5	45.8	30.3	56.1	77.4	41.2	102.0
Excessive sweating									
Average weeks affected per person	5.1	2.1	3.2	3.1	1.7	1.4	0.6	0.3	0.4
Days affected per 1000 days of follow-up	50.9	52.0	50.4	29.5	41.3	22.0	6.3	6.7	6.0

TABLE 20 Days affected by adverse effects (*continued*)

Days affected by adverse effects	A-P			D-P			P-A		
	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16
Fatigue									
Average weeks affected per person	12.5	4.5	8.5	12.1	5.0	7.4	8.9	2.1	7.0
Days affected per 1000 days of follow-up	123.2	111.4	132.0	116.7	122.1	113.8	86.1	49.9	110.6
Headaches									
Average weeks affected per person	1.8	1.1	0.7	5.2	1.4	4.0	1.4	1.0	0.3
Days affected per 1000 days of follow-up	17.7	27.1	11.5	50.2	34.7	60.4	13.2	25.1	5.2
Inability to concentrate									
Average weeks affected per person	2.2	1.1	1.2	0.5	0.3	0.2	2.6	1.2	1.5
Days affected per 1000 days of follow-up	21.9	27.6	18.3	5.0	7.6	3.3	25.5	27.9	23.9
Insomnia									
Average weeks affected per person	3.0	0.9	2.2	4.2	1.8	2.5	0.6	0.2	0.5
Days affected per 1000 days of follow-up	29.2	22.4	33.9	40.3	43.8	38.2	6.2	4.7	7.2
Low mood									
Average weeks affected per person	3.1	1.5	1.7	1.1	0.4	0.7	0.4	0.0	0.4
Days affected per 1000 days of follow-up	31.1	37.8	26.8	10.9	10.3	11.3	3.8	0.2	6.2
Nausea									
Average weeks affected per person	0.7	0.7	0.0	6.8	3.3	3.6	1.0	0.6	0.4
Days affected per 1000 days of follow-up	6.6	16.6	0.0	65.0	81.3	54.7	9.3	14.2	5.9
Oedema									
Average weeks affected per person	2.7	0.1	2.7	5.7	0.9	5.1	9.5	2.6	7.1
Days affected per 1000 days of follow-up	26.7	3.7	42.3	55.1	21.2	77.4	92.2	61.6	113.0
Pruritus									
Average weeks affected per person	0.2	0.2	0.0	3.2	1.2	2.1	2.5	0.6	1.9
Days affected per 1000 days of follow-up	1.9	4.3	0.4	31.1	30.3	31.7	24.3	14.5	31.0

continued

TABLE 20 Days affected by adverse effects (*continued*)

Days affected by adverse effects	A-P			D-P			P-A		
	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16	Overall	Weeks 1–6	Weeks 7–16
Sedation									
Average weeks affected per person	10.5	5.0	5.9	4.0	1.0	3.1	7.9	2.3	5.7
Days affected per 1000 days of follow-up	103.9	12.7	91.5	38.0	24.3	47.1	76.1	54.5	90.8
Vomiting									
Average weeks affected per person	0.4	0.3	0.1	1.5	1.0	0.5	0.1	0.1	0.0
Days affected per 1000 days of follow-up	4.2	8.0	1.7	14.2	23.9	8.0	0.9	1.2	0.8
Weight gain									
Average weeks affected per person	1.6	0.5	1.1	0.8	0.1	0.8	6.2	1.4	4.9
Days affected per 1000 days of follow-up	16.1	13.6	17.9	8.0	2.0	11.9	59.6	33.2	77.5

Chapter 4 Health economics results

Quality of life and quality-adjusted life-years

Table 21 presents EQ-5D utility values at baseline and at 6 and 16 weeks for the three treatment pathways. QALYs were similar for the three groups and equate to approximately 55 days or just under 2 months over a 16-week period.

Table 22 provides a breakdown of EQ-5D-5L responses for each of the five domains of the EQ-5D-5L for participants for whom QALYs were generated. At baseline, no one indicated that they had no pain or discomfort, but this improved at 6 and 16 weeks for all three pathways. Similarly, the proportion of patients with no problems with mobility, usual activities and anxiety or depression also increased over time.

TABLE 21 Mean EQ-5D values and QALYs with 95% bootstrapped CIs for the three treatment pathways

Treatment pathway	Mean EQ-5D values and QALYs (95% bootstrapped CI)			
	Baseline	Week 6	Week 16	QALYs
A-P ($n = 88$)	0.411 (0.352 to 0.466)	0.515 (0.455 to 0.568)	0.509 (0.453 to 0.559)	0.152 (0.136 to 0.167)
D-P ($n = 88$)	0.408 (0.350 to 0.460)	0.551 (0.499 to 0.594)	0.508 (0.448 to 0.562)	0.157 (0.142 to 0.171)
P-A ($n = 87$)	0.420 (0.361 to 0.471)	0.495 (0.438 to 0.545)	0.545 (0.490 to 0.591)	0.152 (0.138 to 0.167)

TABLE 22 EuroQol-5 Dimensions, five-level version, responses by item at baseline and at 6 and 16 weeks

Time point	EQ-5D-5L item	Response, *n* (%)				
		No problems	Slight	Moderate	Severe	Unable to do/extreme
Baseline ($n = 130$)	Mobility	10 (7.7)	26 (20.0)	45 (34.6)	47 (36.2)	2 (1.5)
	Self-care	61 (46.9)	30 (23.1)	23 (17.7)	14 (10.8)	2 (1.5)
	Usual activities	13 (10.0)	33 (25.4)	45 (34.6)	31 (23.8)	8 (6.2)
	Pain/discomfort	0 (0.0)	11 (8.5)	47 (36.2)	59 (45.4)	13 (10.0)
	Anxiety/depression	52 (40.0)	38 (29.2)	23 (17.7)	15 (11.5)	2 (1.5)
A-P						
Week 6 ($n = 88$)	Mobility	13 (14.8)	18 (20.5)	30 (34.1)	26 (29.8)	1 (1.1)
	Self-care	43 (48.9)	20 (22.3)	17 (19.3)	7 (8.0)	1 (1.1)
	Usual activities	14 (15.9)	28 (31.8)	25 (28.4)	18 (20.5)	3 (3.4)
	Pain/discomfort	3 (3.4)	19 (21.6)	46 (52.3)	18 (20.5)	2 (2.3)
	Anxiety/depression	39 (44.3)	20 (22.3)	18 (20.5)	6 (6.8)	5 (5.7)

continued

TABLE 22 EuroQol-5 Dimensions, five-level version, responses by item at baseline and at 6 and 16 weeks (*continued*)

Time point	EQ-5D-5L item	Response, *n* (%)				
		No problems	Slight	Moderate	Severe	Unable to do/extreme
Week 16 ($n = 88$)	Mobility	9 (10.2)	16 (18.2)	38 (43.2)	24 (27.3)	1 (1.1)
	Self-care	43 (48.9)	20 (22.3)	21 (24.7)	3 (3.4)	1 (1.1)
	Usual activities	17 (19.3)	20 (22.3)	33 (37.5)	16 (18.2)	2 (2.3)
	Pain/discomfort	4 (4.5)	16 (18.2)	38 (43.2)	28 (31.8)	2 (2.3)
	Anxiety/depression	42 (47.8)	23 (26.1)	13 (14.8)	9 (10.2)	1 (1.1)
D-P						
Week 6 ($n = 91$)	Mobility	14 (15.9)	17 (19.3)	36 (40.9)	20 (22.3)	1 (1.1)
	Self-care	39 (44.3)	26 (29.5)	16 (18.2)	6 (6.8)	1 (1.1)
	Usual activities	20 (22.3)	19 (21.6)	36 (40.9)	9 (10.2)	4 (4.5)
	Pain/discomfort	4 (4.5)	14 (15.9)	54 (61.4)	16 (18.2)	0 (0.0)
	Anxiety/depression	45 (51.1)	22 (25.0)	16 (18.2)	2 (2.3)	3 (3.4)
Week 16 ($n = 88$)	Mobility	20 (22.3)	11 (12.5)	29 (30.0)	27 (30.7)	1 (1.1)
	Self-care	39 (44.3)	25 (28.4)	15 (17.0)	8 (9.1)	1 (1.1)
	Usual activities	24 (27.3)	18 (20.5)	28 (31.8)	12 (13.6)	6 (6.8)
	Pain/discomfort	3 (3.4)	16 (18.2)	43 (48.9)	23 (26.1)	3 (3.4)
	Anxiety/depression	42 (47.7)	18 (20.5)	18 (20.5)	8 (9.1)	2 (2.3)
P-A						
Week 6 ($n = 87$)	Mobility	12 (13.8)	18 (20.7)	30 (34.5)	26 (29.9)	1 (1.1)
	Self-care	44 (50.6)	22 (25.3)	17 (19.5)	3 (3.4)	1 (1.1)
	Usual activities	17 (19.5)	21 (24.1)	31 (35.6)	13 (14.9)	5 (5.7)
	Pain/discomfort	1 (1.1)	19 (21.8)	37 (42.5)	25 (28.7)	5 (5.7)
	Anxiety/depression	39 (44.8)	24 (27.6)	16 (18.4)	8 (9.2)	0 (0.0)
Week 16 ($n = 87$)	Mobility	14 (16.1)	19 (21.8)	31 (35.6)	22 (25.3)	1 (1.1)
	Self-care	43 (49.4)	21 (24.1)	17 (19.5)	6 (6.9)	0 (0.0)
	Usual activities	18 (20.7)	24 (27.6)	29 (33.3)	11 (12.6)	5 (5.7)
	Pain/discomfort	1 (1.1)	28 (32.2)	41 (47.1)	15 (17.2)	2 (2.3)
	Anxiety/depression	47 (54.0)	15 (17.2)	18 (20.7)	5 (5.7)	2 (2.3)

Resource use

The most commonly accessed resources were prescription services, podiatry, GPs, practice nurses and outpatient appointments (*Table 23*). For those attending accident and emergency, patients could attend between one and four times per period. Hospitalisation duration ranged from one to eight nights, and those patients who attended outpatient appointments could attend up to 12 times per period.

TABLE 23 Total number of patients incurring resource use at 6 and 16 weeks for each treatment pathway

	A-P		D-P		P-A	
Resource use	**Week 6**	**Week 16**	**Week 6**	**Week 16**	**Week 6**	**Week 16**
A&E visit	0	3	1	2	1	4
Hospitalisations	0	1	1	2	2	2
Outpatient	21	23	27	22	24	23
GP surgery visit	13	21	11	14	11	15
GP home visit	1	0	0	1	0	0
GP telephone call	7	5	2	5	6	6
Practice nurse	8	16	15	15	10	9
Practice nurse telephone call	2	3	5	2	2	8
Prescription	50	59	46	38	45	49
Meals on Wheels	0	0	0	0	0	0
Home help	2	2	3	1	3	1
Social worker	0	0	1	0	0	1
Pain management	0	1	5	1	3	0
Physiotherapy	2	3	5	4	4	4
Occupational therapy	1	1	1	0	1	1
Podiatry: NHS	30	34	36	29	36	36
Podiatry: private	3	3	1	1	1	3
Other: NHS[a]	3	2	4	3	1	3
Other: private[a]	1	0	0	0	0	0

A&E, accident and emergency.
a Other services included counsellors, psychiatrists, psychologists, vascular surgery, eye clinic, diabetic clinics and aromatherapy (private).

Table 24 presents a summary of resource use costs for each pathway. Costs were similar across the three pathways, with treatment costs being cheaper for A-P (mean £1424) and slightly more expensive for P-A (mean £1448) and D-P (mean £1452). Similarities were also observed for overall costs, with P-A, on average, having the lowest cost (mean £1942), with the average costs for A-P (mean £2012) and D-P (mean £2032) being slightly higher, but similar.

TABLE 24 Summary of mean treatment cost (95% bootstrapped CIs)

	Mean treatment cost (£) (95% bootstrapped CI)		
Treatment cost	**A-P ($n = 88$)**	**D-P ($n = 88$)**	**P-A ($n = 87$)**
Treatment medications	19 (17 to 21)	33 (29 to 36)	24 (22 to 26)
Treatment visits	1077 (1031 to 1118)	1092 (1047 to 1136)	1096 (1051 to 1140)
Treatment total[a]	1424 (1376 to 1466)	1452 (1405 to 1500)	1448 (1401 to 1493)
Concomitant medications[b]	38 (26 to 58)	24 (15 to 36)	33 (24 to 44)
Other resource use	549 (357 to 963)	555 (377 to 830)	461 (325 to 701)
Total costs	2012 (1808 to 2421)	2032 (1852 to 2304)	1942 (1800 to 2179)

a Treatment total = treatment medications + treatment visits + £328 for laboratory costs, which all patients incurred.
b Further details of the types of concomitant medications are provided in *Appendix 4*.

Order of treatment effect

Regression models were fitted to both costs and QALYs to examine the effect of order of receiving treatment pathways A-P, D-P and P-A. *Table 25* presents the results with 95% bootstrap CIs for the order effect compared with receiving treatments in the first time period. The overall effect of order on costs and QALYs was not significant for the three treatment pathways, although it did approach statistical significance for the A-P pathway, with patients receiving A-P in the third time period more likely to have lower costs than patients receiving A-P in the first time period.

Cost-effectiveness analysis

Table 26 presents a summary of the costs and QALYs over 16 weeks for each of the treatment pathways, as well as the pairwise incremental costs, QALYs and cost per QALY gained. Note that participants were eligible to receive all three treatment pathways. However, participants may drop

TABLE 25 Coefficient showing the mean difference (with 95% bootstrap CIs) in costs or QALYs from receiving treatment second or third compared with first in the crossover study

	Coefficient, mean difference (with 95% bootstrap CIs)	
Treatment pathway	Receiving treatment pathway first vs. second	Receiving treatment pathway first vs. third
A-P		
Cost (£)	−470 (−1230 to 19)	−683 (−1456 to −210)
QALYs	−0.00009 (−0.0362 to 0.0370)	−0.002 (−0.048 to 0.038)
D-P		
Cost (£)	−121 (−570 to 539)	−105 (−555 to 653)
QALYs	0.017 (−0.021 to 0.051)	0.030 (−0.005 to 0.064)
P-A		
Cost (£)	−335 (−799 to 202)	−237 (−681 to 131)
QALYs	−0.007 (−0.044 to 0.032)	−0.018 (−0.058 to 0.023)

TABLE 26 Incremental cost-effectiveness analysis with 95% bootstrap CIs

Analysis	Cost (£)	QALY
A-P ($n = 88$)	2012 (1808 to 2421)	0.152 (0.136 to 0.167)
D-P ($n = 88$)	2032 (1852 to 2304)	0.157 (0.142 to 0.171)
P-A ($n = 87$)	1942 (1800 to 2179)	0.152 (0.138 to 0.167)
Pairwise mean incremental		
A-P vs. D-P ($n = 67$)	−113 (−360 to 102)	−0.002 (−0.011 to 0.007)
A-P vs. P-A ($n = 67$)	154 (−64 to 510)	0.006 (−0.002 to 0.014)
D-P vs. P-A ($n = 73$)	149 (−25 to 366)	0.007 (0.0002 to 0.015)
Pairwise mean ICER (£)		
A-P vs. D-P ($n = 67$)		7021 (24,715 to 37,038)
A-P vs. P-A ($n = 67$)		7482 (−27,623 to 49,221)
D-P vs. P-A ($n = 73$)		94,136 (28,076 to 232,390)

out of the study before receiving all three pathways. Therefore, 67 participants received A-P and D-P, 67 participants received A-P and P-A and 73 participants received D-P and P-A. The incremental QALY gain is small and is uncertain when comparing A-P with D-P and A-P with P-A. However, there is a gain for those on the D-P pathway, equating to approximately 2.5 days when comparing D-P with P-A. The incremental cost gain was not significant for any comparison and ranged between a mean of −£113 for A-P compared with D-P and a mean of £154 for A-P compared with P-A. *Figure 14* shows the cost-effectiveness planes for each pathway comparison. On average, D-P is more costly and less effective than A-P, with 57% of points being in the south-west quadrant of the cost-effectiveness plane (mean ICER £7026). A-P and D-P were, on average, more costly but more effective than P-A, with the majority of points being in the north-east quadrant of the cost-effectiveness plane (A-P vs. P-A mean

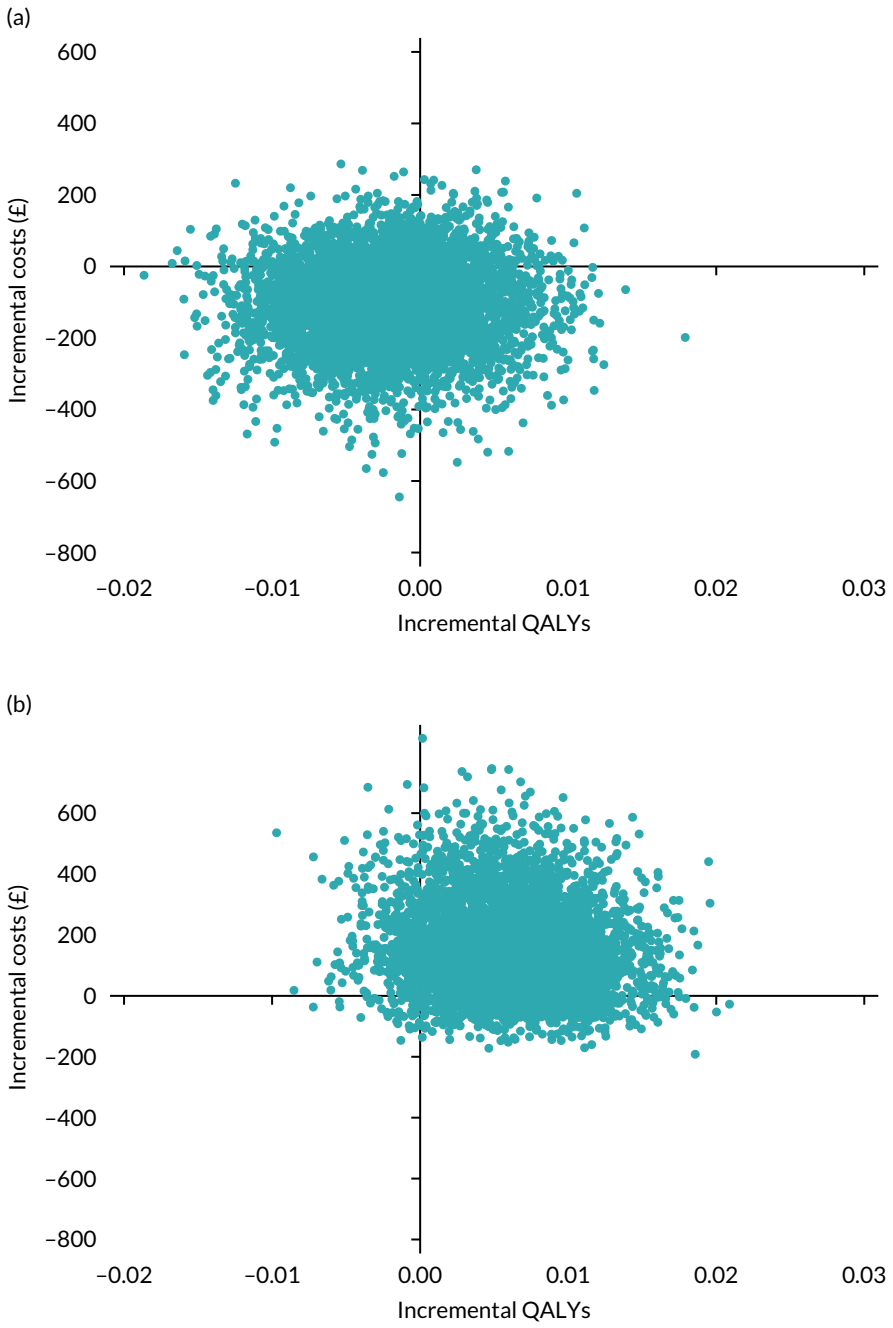

FIGURE 14 Incremental cost-effectiveness plane. (a) A-P vs. D-P; (b) A-P vs. P-A; and (c) D-P vs. P-A. (*continued*)

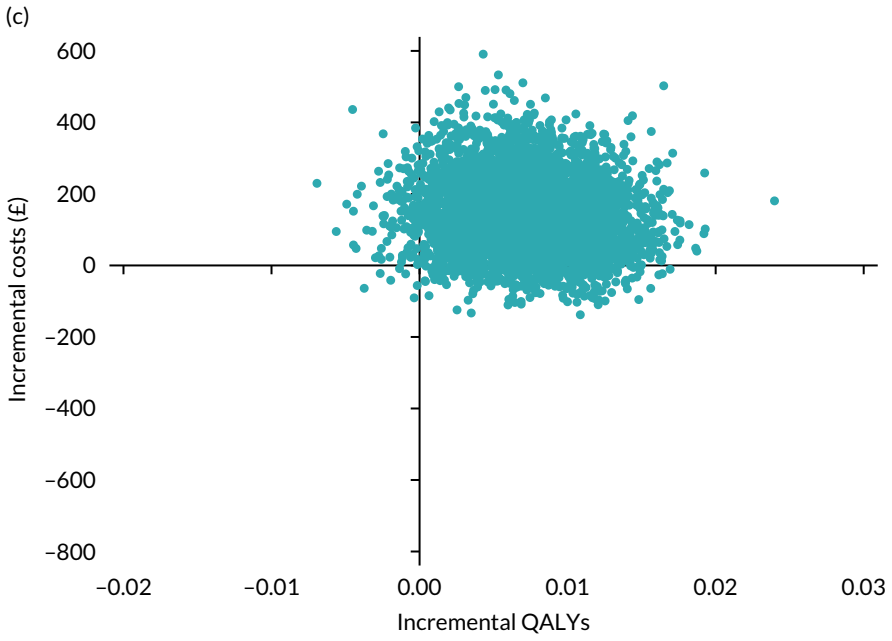

FIGURE 14 Incremental cost-effectiveness plane. (a) A-P vs. D-P; (b) A-P vs. P-A; and (c) D-P vs. P-A.

ICER £7441, 79% in north-east quadrant; D-P vs. P-A mean ICER £94,157, 91% points in the north-east quadrant, respectively) (*Figure 15*). For all comparisons, it is important to note that they are based on a small QALY gain and a small difference in costs between the two treatment pathways.

Sensitivity analysis

Non-pairwise comparisons of the three treatment pathways gave ICERs of £4000 for A-P compared with D-P (with D-P on average being more costly but more effective), −£700,000 for A-P compared with P-A (with P-A being less costly and more effective) and £18,000 for D-P compared with P-A (with P-A being less costly and less effective). The incremental QALY difference is very small and uncertain, which is reflected in the difference in the ICERs between pairwise and non-pairwise comparisons.

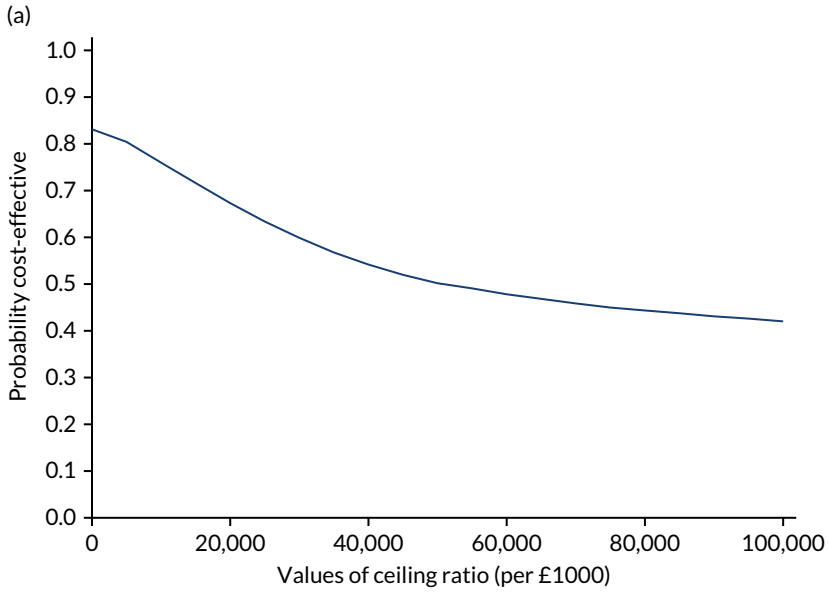

FIGURE 15 Cost-effectiveness acceptability curve. (a) A-P vs. D-P; (b) A-P vs. P-A; and (c) D-P vs. P-A. (*continued*)

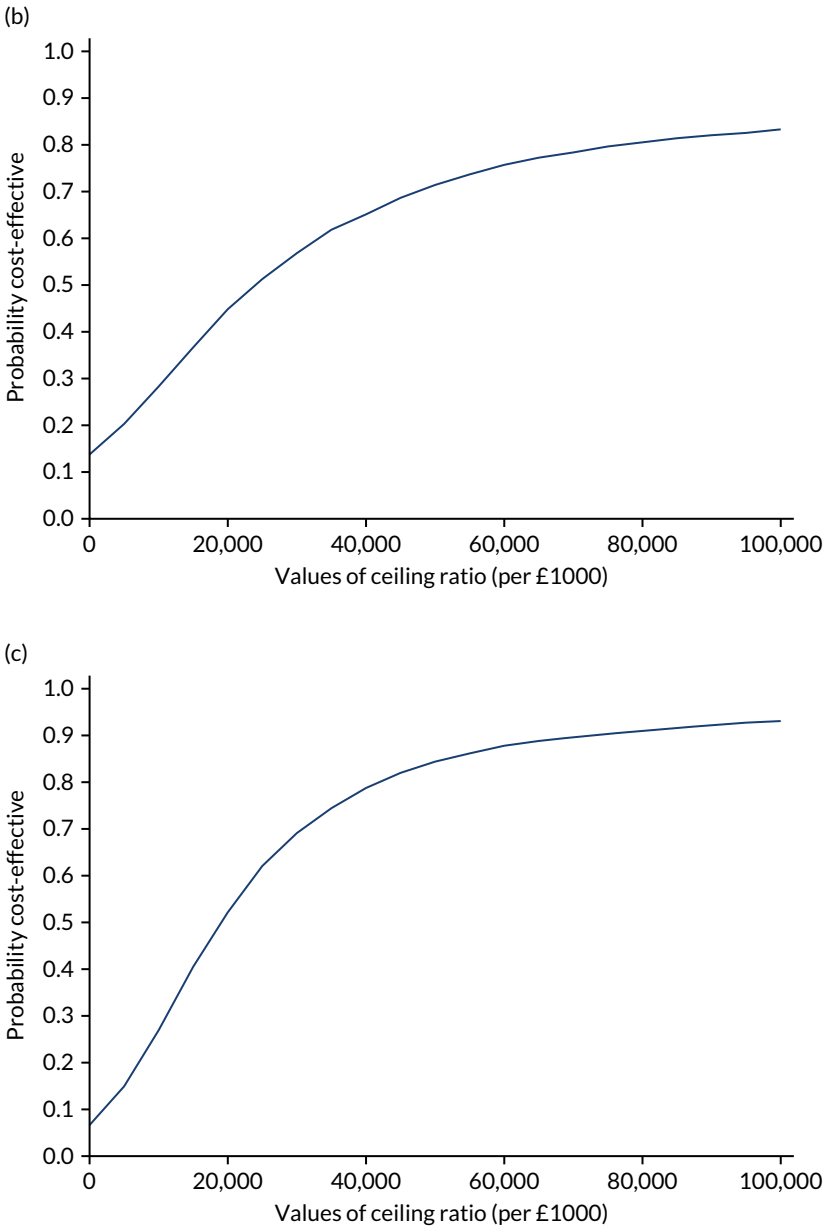

FIGURE 15 Cost-effectiveness acceptability curve. (a) A-P vs. D-P; (b) A-P vs. P-A; and (c) D-P vs. P-A.

EuroQol-5 Dimensions, five-level version, Devlin algorithm

Table 27 presents EQ-5D utility values at baseline and at 6 and 16 weeks for the three treatment pathways for the crosswalk and Devlin algorithm. Utilities and QALYs were higher for the Devlin algorithm than the crosswalk, as observed elsewhere,[78] but were similar across the three groups for both methods.

The D-P and P-A pathways become less cost-effective, compared with A-P, when the Devlin algorithm is used to estimate the EQ-5D-5L (A-P vs. D-P mean ICER –£37,784 and A-P vs. P-A mean ICER £31,909), with the ICER for D-P compared with P-A being lower (mean ICER £13,097). However, there remains uncertainty in the cost-effectiveness of all pathways.

Including costs borne by participants and their carers

Participants were asked about additional costs, including costs relating to help, transport, changes to the home, specialist equipment, time off work, loss of pay and help from friends and relatives over the

TABLE 27 Mean EQ-5D values and QALYs with 95% bootstrapped CIs for the three treatment pathways for crosswalk and Devlin algorithm

Analysis	Treatment pathway	Mean EQ-5D values and QALYs (95% bootstrapped CI)			
		Baseline	Week 6	Week 16	QALYs
Crosswalk	A-P	0.411 (0.352 to 0.466)	0.515 (0.455 to 0.568)	0.509 (0.453 to 0.559)	0.152 (0.136 to 0.167)
	D-P	0.408 (0.350 to 0.460)	0.551 (0.499 to 0.594)	0.508 (0.448 to 0.562)	0.157 (0.142 to 0.171)
	P-A	0.420 (0.361 to 0.471)	0.495 (0.438 to 0.545)	0.545 (0.490 to 0.591)	0.152 (0.138 to 0.167)
Devlin algorithm	A-P	0.506 (0.445 to 0.564)	0.601 (0.537 to 0.655)	0.595 (0.535 to 0.648)	0.179 (0.162 to 0.194)
	D-P	0.507 (0.446 to 0.561)	0.653 (0.600 to 0.698)	0.599 (0.534 to 0.657)	0.187 (0.171 to 0.201)
	P-A	0.511 (0.449 to 0.566)	0.592 (0.529 to 0.645)	0.642 (0.581 to 0.691)	0.183 (0.166 to 0.197)

past 8 weeks (*Table 28*). The largest costs were those where adaptions to the home were needed, although this affected only two participants, and costs incurred from caring support from friends and relatives, which were needed by 40–50% of participants.

Over the three treatment pathways, the mean costs borne by participants are more than double the other costs reported for the CSRI (see *Table 28*) and these were £1207 (95% bootstrap CI £758 to £2376) for A-P, £1740 (95% bootstrap CI £1077 to £3309) for D-P and £2138 (95% bootstrap CI £881 to £6836) for P-A. Overall costs per pathway also increased and these were £2670 (95% bootstrap CI £2220 to £3840) for A-P, £3216 (95% bootstrap CI £2561 to £4807) for D-P and £3619 (95% bootstrap CI £2358 to £8322) for P-A (*Table 29*). The inclusion of costs to participants and their carers did change the mean ICERs, although the results remained uncertain. D-P was more expensive and less effective than A-P (mean ICER −£19,268). P-A was more costly and more effective than both A-P (mean ICER £21,405) and D-P (mean ICER £229,855), respectively.

TABLE 28 Costs borne by participants and their carers

Cost	A-P		D-P		P-A	
	Week 6	Week 16	Week 6	Week 16	Week 6	Week 16
Employed extra help	5; 142 (71 to 212)	4; 160 (160 to 160)	6; 180 (0 to 453)	5; 198 (40 to 356)	5; 359 (0 to 810)	3; 60 (0 to 277)
Transport to health-care appointments	7; 22 (5 to 39)	6; 32 (0 to 74)	7; 10 (0 to 26)	5; 17 (0 to 34)	4; 152 (0 to 2032)	0; N/A
Transport to pain clinics	0; N/A	5; 20 (0, 45)	2; 30 (N/A)	2; 20 (N/A)	2; 20 (N/A)	1; 0 (N/A)
Adaption to the home	2; 1013 (N/A)	2; 615 (N/A)	2; 1690 (N/A)	0; N/A	1; 3000 (N/A)	0; N/A
Specialist equipment	1; 40 (N/A)	1; 280 (N/A)	1; 600 (N/A)	1; 150 (N/A)	2; 840 (N/A)	2; 325 (N/A)
Other costs[a]	2; 172 (N/A)	2; 150 (N/A)	0; N/A	1; 10 (N/A)	2; 80 (N/A)	1; 80 (N/A)

TABLE 28 Costs borne by participants and their carers (*continued*)

	A-P		D-P		P-A	
Cost	**Week 6**	**Week 16**	**Week 6**	**Week 16**	**Week 6**	**Week 16**
Employment, *n* (%)						
Currently employed	24 (25.3)	20 (22.0)	26 (28.6)	24 (26.7)	26 (26.5)	23 (25.6)
Full time	15 (62.5)	15 (75.0)	18 (69.0)	16 (66.7)	17 (65.4)	17 (73.9)
Part time	8	5	7	7	8	6
Missing	1	0	1	1	1	0
Time off in the last 8 weeks	2	0	3	1	3	3
Sick leave	1	0	1	0	1	2
Paid holiday	1	0	2	1	1	0
Unpaid leave	0	0	1	1	0	0
Made up time[b]	0	0	2	0	0	0
Other	1	0	0	0	1	1
Total cost (£) of lost earnings (95% CI)	3.82 (0 to 1140)	0.00	19.71 (0 to 47.80)	11.96 (0 to 35.71)	73.27 (0 to 209.22)	112.83 (0 to 278.01)
Help needed from a friend or relative, *n* (%)						
Help from friend or relative	42 (44.2)	39 (43.3)	45 (51.1)	36 (40.5)	47 (47.5)	38 (42.2)
With personal care	16	15	17	16	19	17
With childcare	2	3	2	1	1	3
With housework	36	25	33	28	30	27
With transport	25	20	20	19	29	22
With general support	32	29	38	28	33	31
With other	4	2	1	5	2	1
Friend/relative stayed off work to help	2	1	2	2	1	0
Total cost (£) of time lost for friend/relative (95% CI)	3418 (369 to 6467)	1840 (790 to 2890)	1439 (822 to 2055)	1289 (578 to 2000)	1820 (978 to 2662)	3385 (670 to 6100)
Total costs (£) to participants (95% CI)	3456 (406 to 6505)	1860 (808 to 2913)	1512 (883 to 2142)	1315 (601 to 2029)	1962 (1107 to 2818)	3508 (778 to 6238)

N/A, not appliable.

a Other costs specified by participants included transport and parking, a gardener, massage, chiropody, scooter, automatic car, footwear and a Zimmer frame.

b Worked extra hours to compensate for time off rather than take that time off as leave.

Note

Data reported are *n*; total cost (£) (95% bootstrap CI) unless specified otherwise.

TABLE 29 Summary of sensitivity analysis results

Analysis	Incremental costs (£) (95% bootstrap CI)	Incremental QALYs (95% bootstrap CI)	ICER (£)
Main analysis			
A-P vs. D-P ($n = 67$)	−113 (−360 to 102)	−0.002 (−0.011 to 0.007)	7021 (−24,715 to 37,038)
A-P vs. P-A ($n = 67$)	154 (−64 to 510)	0.006 (−0.002 to 0.014)	7482 (−27,623 to 49,211)
D-P vs. P-A ($n = 73$)	140 (−25 to 366)	0.007 (0.0002 to 0.015)	94,136 (28,082 to 232,450)
Sensitivity analysis: Devlin algorithm			
A-P vs. D-P ($n = 67$)	−113 (−360 to 102)	−0.004 (−0.014 to 0.006)	−37,784 (−167,464 to 23,057)
A-P vs. P-A ($n = 67$)	154 (−64 to 510)	0.005 (−0.004 to 0.013)	31,909 (6018 to 71,866)
D-P vs. P-A ($n = 73$)	140 (−25 to 366)	0.008 (0.0009 to 0.015)	13,097 (−23,614 to 48,170)
Sensitivity analysis, including costs borne to participant and carers			
A-P vs. D-P ($n = 67$)	−835 (−3172 to −46)	−0.002 (−0.011 to 0.007)	−19,268 (−113,402 to 48,584)
A-P vs. P-A ($n = 67$)	−968 (−4727 to 1055)	0.006 (−0.002 to 0.014)	21,405 (−81,327 to 125,782)
D-P vs. P-A ($n = 73$)	−432 (−3718 to 1650)	0.007 (0.0002 to 0.015)	229,855 (−17,691 to 698,208)
Sensitivity analysis: multiple imputation of missing EQ-5D responses			
A-P vs. D-P ($n = 130$)	17.98 (−214 to 305)	−0.004 (−0.009 to 0.002)	−25,184 (−69,553 to 10,661)
A-P vs. P-A ($n = 130$)	−93.13 (−399 to 196)	0.004 (−0.0004 to 0.009)	−4615 (−56,525 to 38,410)
D-P vs. P-A ($n = 130$)	−114 (−402 to 139)	0.008 (0.003 to 0.127)	56,862 (1701 to 122,604)

Multiple imputation of missing EuroQol-5 Dimensions responses

Imputing the EQ-5D responses increased the sample size to 130 (i.e. the full sample who participated in the study). On average, this increased the QALYs for A-P (mean QALY 0.157, 95% bootstrap CI 0.145 to 0.168) and D-P (mean QALY 0.160, 95% bootstrap CI 0.149 to 0.171) compared with the observed cases (see *Table 26*). However, the mean QALY for P-A remained similar to that prior to imputing the data (mean QALY 0.152, 95% bootstrap CI 0.141 to 0.164). As with other sensitivity analysis, imputing missing values did change the mean ICERs, with results remaining uncertain.

Chapter 5 Discussion

Main findings

The OPTION-DM trial showed that all three treatment pathways (i.e. A-P, D-P and P-A) were equally effective in reducing neuropathic pain intensity, significantly reducing the baseline NRS score from a baseline mean of 6.6 (SD 1.5) points to an average of 3.3 (SD 1.8) points at 16 weeks. There were no differences between the treatment pathways, as the effects observed were not different statistically or clinically different between the pathways, with the CIs for the primary end point (i.e. pain at week 16) having the prespecified difference only at their very edge.

As the three treatment options produced similar pain control, it might be important to consider other outcomes when deciding which treatment to recommend; however, no one treatment was uniformly preferable across the end points we assessed.

The P-A pathway led to the fewest discontinuations on monotherapy due to AEs ($p = 0.031$) and numerically was the most preferred pathway (A-P, 24%; D-P, 33%; P-A, 43%; $p = 0.27$) at the end of the trial. This is consistent with the American Academy of Neurology recommendations, which give only pregabalin level A evidence, mainly because completion rates in pregabalin trials were more than 80%.[79] The P-A pathway also gave the best pain relief for higher levels of baseline depression ($p = 0.011$) and both the P-A and D-P pathways provided better pain relief than the A-P pathway for higher levels of baseline anxiety ($p = 0.016$).

The trial explored a number of secondary end points. The head-to-head trial of maximum tolerated doses of amitriptyline, duloxetine and pregabalin showed similar efficacies for all three monotherapies at the end of 6 weeks, although there were fewer discontinuations due to treatment-emergent AEs with pregabalin. However, only in one-third of patients did monotherapy achieve mild pain (i.e. 'responders', with a NRS score of ≤ 3). Similarly, monotherapy achieved 50% pain relief in around 40% of patients. Most patients ('non-responders') required combination treatment, which resulted in a 0.6-point further improvement in NRS score and 18% and 14% increases in the achievement of a NRS score of ≤ 3 points and 50% pain relief, respectively. In a crossover trial, Gilron *et al.*[57] studied 56 patients with neuropathic pain (40 patients with DPNP) treated to maximum tolerated doses of gabapentin, nortriptyline and their combination over 1-month treatment periods. They found that combination treatment was more efficacious than either drug alone. Another crossover trial[80] ($n = 73$), of 5-week treatment periods, compared the combination of imipramine and pregabalin at moderate doses with either treatment on its own in painful polyneuropathy. The study found that combination treatment was more efficacious in relieving neuropathic pain than either drug on its own, but resulted in higher rates of side effects. Despite these results, currently, a number of international bodies do not recommend combination treatment for DPNP because of 'insufficient evidence'.[81–83] Although the OPTION-DM trial was not designed as a comparison of monotherapy and combination treatment, the data make a compelling case for the recommendation of combination treatment of first-line drugs for DPNP patients with suboptimal response to a monotherapy.

Despite massive variations in the cost and availability of amitriptyline, duloxetine and pregabalin in many countries, it is reassuring that all three drugs are equally efficacious in relieving pain. Furthermore, all monotherapies resulted in a substantial improvement of QoL domains, sleep and measures of mood from baseline. However, amitriptyline was significantly better than duloxetine in improving physical functioning and sleep, and pregabalin was superior to duloxetine in improving role limitation due to physical health. Treatment-emergent AEs were predictable for the monotherapies, although there were no significant differences in their overall frequency and severity. This may, in part,

be due to the use of maximum tolerated doses rather than a fixed treatment regime. There were also no significant differences in the frequency of SAEs. However, compared with some previous studies, combination treatment with maximum tolerated doses was well tolerated, with few treatment-emergent AEs, except for larger numbers of patients reporting diarrhoea and dry mouth in the A-P pathway.

Health economics

To the best of our knowledge, this study is the first to present the results of a head-to-head comparison of current medications and their combinations in an economic evaluation over a 16-week period. QALYs were similar over the study time period, with an average difference in costs ranging from −£113 to £154 across the three comparisons. Ninety-five per cent bootstrap CIs around costs and QALYs demonstrated the uncertainty in results. Furthermore, the study showed that greater costs are borne by the patients and their carers rather than the NHS.

Wu *et al.*[32] examined the cost-effectiveness of duloxetine compared with usual care over a 52-week period. Wu *et al.*[32] looked at three perspectives and found incremental costs slightly higher than those for our study [i.e. direct (closest possible to NHS) US$1600 (£1194); employment and direct US$2196 (£1639) and societal, direct and employment US$2754 (£2056)]. However, in addition to looking at single rather than combination therapy, the time period is longer in the Wu *et al.*[32] study and the health-care system is different in the USA and, therefore, caution should be given when comparing these results with those from the OPTION-DM trial.

Two further studies[33,34] looked at duloxetine in decision-analytic models. O'Connor *et al.*[34] presents the cost per QALY of duloxetine compared with desipramine at US$47,700 (or £35,609). This is higher than our average QALY for A-P compared with D-P (£7026) and lower than the average QALY for D-P compared with P-A (£94,157), although it should be noted, again, that this is not a combination therapy study and the time period is shorter and so not comparable. It should also be noted that the O'Connor *et al.*[34] results were sensitive to obtaining pain relief. Beard *et al.*[33] also fitted a decision-analytic model and noted a saving of £77,071 for every 1000 patients treated in 2007 or £109,246 per 1000 patients in 2019.

Finally, de Salas-Cansado *et al.*[35] compared pregabalin with usual care from a Spanish NHS and societal perspective over a 23-week period. The costs per QALY were higher than those for our study [i.e. €5302 (£4426) societal and €14,381 Spanish NHS (£12,005)].

Also worth noting is that the utility values for our sample do appear to be low in comparison with those for the general diabetes population. *Table 3* presented mean utility values for the EQ-5D at baseline and at 6 and 16 weeks, and these ranged between 0.408 and 0.551. Collado Mateo *et al.*[84] present normative values for a Spanish diabetes population by age and sex. The mean EQ-5D values for people aged 60–69 years (the most comparable age band to our population mean of 61.8 years) were 0.860 for males and 0.745 for females, respectively. The authors used the Spanish crosswalk rather than UK crosswalk to obtain utilities for the EQ-5D, but other studies also suggest higher utility values. For example, Wang *et al.*[85] report a mean utility of 0.720 for patients in Singapore with type 2 diabetes mellitus. Likewise, in a Chinese study, Pan *et al.*[86] report a mean value of 0.862 for patients with type 2 diabetes mellitus and a mean of 0.815 if the patients also had neuropathy.

Strengths and weaknesses of the research

To the best of our knowledge, this was the first randomised double-blind comparator trial of neuropathic pain treatment pathways. Although head-to-head trials of individual monotherapies and combination treatments could be designed, investigating treatment pathways as a whole was felt most

efficient and applicable to current clinical practice. This is because most patients are started on a monotherapy and will require a second agent to be added in combination within a few months. Therefore, the OPTION-DM trial reflected current practice, allowing the outcomes of this study to be readily generalisable. Recruitment from a wide array of sites, including primary and secondary care, further strengthens the generalisability of the study.

The initial prespecified number of participants was not recruited, and this could be taken as a limitation of the study. Early monitoring of the fidelity of recruitment revealed that recruitment for this demanding trial was challenging. Rather than compromise the integrity of the trial, and with the approval of the independent TSC and head of the Health Technology Assessment, the trial continued to a fixed time point when an adequate sample size had been achieved to detect a difference of at least 1 NRS point. The onset of the COVID-19 pandemic further affected follow-up, with some participants having a curtailed follow-up in the final pathway. A strength of the OPTION-DM trial was that, although the trial was curtailed in terms of recruitment, to the best of our knowledge, it is still the longest and largest crossover combination trial. Given the results, and that a 0.5-point NRS difference was at the very edge of plausible difference between the treatment arms, even a significantly larger sample size would probably not have altered study outcomes or conclusions.

The lack of a placebo arm can also be taken as a limitation of the study. However, given the existing wealth of evidence from previous placebo-controlled trials and the advice from our PPI panel, we decided against a placebo control, as including a placebo control would have made the trial longer, more complicated (i.e. a four-way crossover trial) and it would not have been ethically justifiable to leave participants on placebo alone for 17 weeks. The number of dropouts within the 1–2 weeks prior to randomisation in this trial suggest that such a trial is not feasible. The lack of a placebo arm means that we cannot attribute the change from baseline solely to the introduction of treatment, as some improvement may be due to regression to the mean. Nonetheless, previous trials[14–22] have demonstrated far smaller changes in participants treated with placebo, and it is reasonable to assume that most of the improvement is due to therapy.

The EQ-5D was captured prior to treatment pathway 1, but not prior to treatment pathways 2 and 3, and was captured for each treatment pathway at 6 and 16 weeks. It may be that measuring HRQoL more frequently would more likely capture any disutilities associated with AEs, and any future study should consider this. The economic analysis reports the within-trial results over 16 weeks, and this is in line with other published economic evaluations,[31,32] although future studies could consider modelling the cost-effectiveness over a longer time frame.

There are two further limitations of the economic evaluation. First, the use of a questionnaire to capture resource use means that resource use is self-reported and could be subject to recall issues, thereby potentially underestimating the overall cost of each treatment pathway. The capturing of resource use information from routine sources could be considered in future studies. Second, the crossover nature of this study lent itself to a pairwise comparison of the alternative treatment pathways. This pairwise comparison was varied in a sensitivity analysis, which, owing to the small difference in costs and QALY, meant that the results remained uncertain.

Evidence in the context of other existing research

The OPTION-DM trial was an efficiently designed head-to-head crossover trial,[2] with each patient undergoing all three pathways over 50 weeks, making it, to the best of our knowledge, the longest blinded neuropathic pain trial. The durations of monotherapy and combination treatment were long enough to assess full treatment effects.[37] Previous combination trials mainly used fixed-dose titration regimens regardless of treatment response.[31,80] This does not reflect clinical practice and often resulted in high dropout rates.[31] The present trial employed a flexible dosing regimen to achieve maximum

tolerated doses, based on individual responses. Moreover, all previous DPNP multiperiod crossover trials were smaller.[25–27] In addition, other studies included neuropathic pain conditions other than DPNP.[29,57,80] Finally, most previous trials did not use combinations of current first-line drugs.[29,57,80] The OPTION-DM trial tried to obtain robust data from current first-line drugs, as, based on the trajectory of new drug developments for DPNP over the past 25 years, the emergence and use of revolutionary new drugs that are considerably more efficacious than current ones seemed unlikely over the foreseeable future.

Implications for practice and policy

The OPTION-DM trial has demonstrated that all three treatment pathways and monotherapies are equally efficacious. Although most international painful diabetic neuropathy management guidelines, including the one by NICE (CG96, updated in 2021),[82] place the monotherapies as first-line agents, based on indirect comparisons of the treatments' efficacy, this is, to the best of our knowledge, the first time that an adequately designed head-to-head comparator trial has been undertaken, and it confirmed that the treatments are of equivalent efficacy. The OPTION-DM trial will hopefully reduce the ambiguity of indirect comparisons that, for example, led the French panel of experts to recommend pregabalin as a second-line agent.[87]

Combination treatment is currently not recommended by international guidelines because of insufficient evidence.[81–83] NICE guidance,[82] which was updated in 2021, recommends switching to a different treatment rather than combination treatment. In this trial, only one-third of patients saw a reduction in pain to 'mild' as quantified as a NRS score of ≤ 3 points ('responders'). Similarly, monotherapy achieved 50% pain relief in around 40% of patients. Many patients ('non-responders') required combination treatment that resulted in a further mean improvement of 1 point on the NRS and an additional 18% and 14% increase in the achievement of NRS score of ≤ 3 points and 50% pain relief, respectively. Although the OPTION-DM trial was not designed as a comparison of monotherapy and combination treatment, the data make a compelling case for the recommendation of combination treatment of first-line drugs for DPNP patients with suboptimal response to a monotherapy, particularly as combination treatment was very well tolerated.

In clinical practice, patients are sometimes prescribed very high doses of amitriptyline (up to 150 mg/day) and, therefore, it is no great wonder that so many patients experience unwanted side effects. The OPTION-DM trial has shown that titration to 60 mg per day can be effective. The OPTION-DM trial also found that the mean dose per day (% on maximum dose) of amitriptyline, duloxetine and pregabalin at week 6 was 60 mg (59%), 82 mg (53%) and 396 mg (56%), respectively. For patients on combination treatments A-P, D-P and P-A the mean dose per day (% on maximum dose) of add-on drug at week 16 was 365 mg (47%), 407 mg (55%) and 55 mg (47%), respectively. These data show that only around half of patients will tolerate maximum doses of these drugs, and this is in the context of a clinical trial that excluded patients with major comorbidities. A key message from the OPTION-DM trial is that drugs need to be titrated gradually, over at least 2 weeks and, in some patients (for example the elderly and those with comorbidities) even more slowly, factoring in the side effect profile and the severity of side effects, as well as efficacy.

The data from OPTION-DM trial are powerful. The OPTION-DM trial was, to the best of our knowledge, the longest blinded neuropathic pain trial to date. Unlike previous combination treatment crossover trials,[37] the durations of monotherapy and combination treatments were long enough to assess full treatment effects. Moreover, previous combination trials[31,80] mainly used fixed-dose titration regimens regardless of treatment response, which does not reflect clinical practice and resulted in high dropout rates. The OPTION-DM trial employed a flexible dosing regimen to achieve maximum

tolerated doses, based on individual responses. Moreover, all previous DPNP multiperiod crossover trials[25–27] had smaller sample size and other studies[29,57,80] included neuropathic pain conditions other than DPNP. In addition, most previous trials did not use combinations of current first-line drugs. Therefore, the robustness of OPTION-DM trial data will probably influence clinical practice, guidelines and commissioners.

Implications for health care

The current NICE guideline (CG173)[82] for the management of painful DPNP states:

> *Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain.*
>
> *If initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are not effective or not tolerated.*
>
> *© NICE 2020 Neuropathic Pain in Adults: Pharmacological Management in Non-Specialist Settings.*[82] *Available from www.nice.org.uk/guidance/cg173. All rights reserved. Subject to Notice of rights NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication*

The OPTION-DM trial was a pragmatic trial reflecting current best-treatment practice and examined three treatment pathways for painful diabetic neuropathy. In each treatment pathway, patients were initially commenced on monotherapy followed by combination therapy. The results showed significant improvements in pain severity in all three treatment pathways. In addition, the results showed that combination treatment is not only safe but also necessary for a significant proportion of patients to achieve meaningful pain relief (i.e. a NRS pain score of ≤ 3 points).

The most recent NICE CG173 guideline[82] recommends that patients switch to a second or third agent if initial/subsequent monotherapy is ineffective. In practice, this often results in poor patient satisfaction and disillusionment, as well as failure to achieve adequate pain relief due to treatment inertia. The results of the OPTION-DM trial suggest that combination treatment may be advocated if inadequate pain relief is achieved with monotherapy. To facilitate this, future pharmacotherapy guidelines for painful diabetic neuropathy should be rationalised into treatment pathways, as the majority of patients end up having combination treatments. Our cost-effectiveness analysis shows that there are no differences between the treatment pathways assessed. Further post hoc analyses are being planned to examine if certain subgroups of patients (e.g. the elderly, patients with mood disorders or clinical pain phenotypes) respond better to a particular treatment pathway.

Recommendations for future research

Implementation

There remains a clinical and economic need to improve outcomes in patients with painful diabetic neuropathy. Based on the trajectory of new drug developments for painful diabetic neuropathy over the past 25 years, the emergence and use of new drugs that are more efficacious than current ones seems unlikely in the next decade. In the OPTION-DM trial, around 40% of patients achieved significant improvement in pain (i.e. 30% improvement in NRS or a NRS score of ≤ 3 points) based on simple pragmatic guidance to treatment escalation. There is, however, a wide variation in treatment outcomes across England. We need to explore the differences in clinical practice and patient behaviour that underlie these differences, as well as promote the outcomes of the OPTION-DM trial.

Mechanistic approach

In all treatment pathways, there was a wide variation in NRS pain intensity scores, with some patients showing marked improvement and others showing minimal or no improvement. Further research is needed to explain why some patients do so well, whereas others do not. This research would involve detailed clinical phenotyping of patients using recent innovations in magnetic resonance neuroimaging, quantitative sensory assessment and genotyping. This research might uncover underlying pain mechanisms that inform treatment responses in individual patients.

Holistic approach

It is notable that we found a significant relationship between emotional distress (e.g. anxiety and depression) and improvement in pain scores in two of the three treatment pathways assessed. The precise role of psychosocial factors in explaining pain severity, distress and treatment response are not well understood. Most studies have investigated psychosocial and biomedical variables independently and the differing contributions of these variables on treatment outcomes are poorly specified.

Pharmacological and non-pharmacological approaches

A significant proportion (around 50%) of patients are not helped by any treatment pathway and this raises the question of 'what next?'. NICE recommends tramadol only if rescue therapy is needed, but often patients are commenced and remain on long-term opioid therapy. The safe use of opioids and other pharmacological [e.g. high-dose (8%) capsaicin patch or intravenous lidocaine therapy] and non-pharmacological (e.g. spinal cord stimulation) treatments for painful diabetic neuropathy should be explored further.

Chapter 6 Conclusions

The results of the OPTION-DM trial showed that all three treatment pathways had equal pain control, in terms of both statistical and clinical significance. The P-A pathway led to fewer monotherapy discontinuations due to treatment-emergent AEs and was also most preferred by participants at the end of the trial, suggesting that this may be the safest choice as a first line of therapy. Importantly, although the trial was not primarily designed to examine the benefit of combination treatment when there is suboptimal response to a monotherapy, this pragmatic trial demonstrated that combination treatment, where needed, was well tolerated and can lead to further reduction in pain following the introduction of second-line therapy.

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Publications

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Data-sharing statement

Requests for patient-level data and statistical code should be made to the corresponding author and will be considered on a case-by-case basis following the principles for sharing patient-level data.[88]

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Case report form completion schedule

Form	Pre-screening	Week			Repeat through each pathway: week															Week 17	Unscheduled forms	Study discontinuation
		−2	−1	0 (randomisation)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Pre-screening log	✗																						
Screening consent		✗																					
Demographics		✗																					
Medical history		✗																					
Vital signs		✗																		✗			
mTCNS		✗																					
DN4		✗																					
Laboratory tests		✗																		✗			
Previous medications		✗																					
Weekly contact form			✗					✗	✗		✗[a]	✗[a]		✗	✗	✗	✗	✗	✗				
Pregnancy test[b]				✗			✗			✗			✗							✗			
Confirmation of eligibility				✗																			
Randomisation				✗																			
Treatment decisions					✗	✗	✗			✗	✗[c]	✗[c]	✗[c]										
Treatment compliance log						✗	✗			✗		✗[c]	✗							✗	✗		✗
Concomitant medications																					✗		
AEs																					✗		
Unblinding																					✗		
Unscheduled dose changes																					✗		
Pregnancy information																					✗		
Protocol non-compliance																					✗		
Intervention withdrawal																					✗		✗
Study completion discontinuation																				✗[d]			✗[d]

a Only relevant for 'responders' continuing on first-line treatment as monotherapy.
b For women of childbearing potential only.
c Participants on second-line treatment only.
d Required at end of study (week 17) or if a participant stops all study involvement early.

Appendix 2 Questionnaire completion schedule

Form/event	Week		Repeat through each pathway: week		Study discontinuation
	−2	0 (randomisation)	6	16	
Assessment of suicidal risk[a]	✗				
Pain diary[b]	✗				
BPI-MSF		✗	✗	✗	✗
ISI		✗	✗	✗	✗
NPSI		✗	✗	✗	✗
HADS		✗	✗	✗	✗
SF-36		✗	✗	✗	✗
EQ-5D-5L		✗	✗	✗	✗
CSRI		✗	✗	✗	✗
Pain Catastrophizing Scale		✗			
Tolerability Scale		✗	✗	✗	✗
Study medicine and pain diary[c]		✗	✗	✗	✗
PGIC				✗	✗

a Assessment of Suicidal Risk Questionnaire can be self-completed by the participant or it can be administered by the study team.
b Pain diary to be given out at week −2 and completed by the participant daily between weeks −2 and 0.
c Study medicine and pain diary to be given out at each study visit and completed by the participant daily throughout the study.

Appendix 3 Summary of protocol amendments

Amendment number	Summary of amendment
Substantial amendment 1, protocol version 3.0, approved 24 March 2017 (REC only)	Patient-perceived tolerability end points added. Scoring system for SF-36 updated and HADS end points updated. Inclusion criteria clarified: • Confirmed that pain does not need to be daily, but must be neuropathic pain affecting both feet • Amended the version of the Toronto Clinical Neuropathy Score to the modified version Exclusion criteria clarified: • Clarified that investigator judgement should be used when assessing the exclusion criteria for alcohol/substance abuse, history of severe psychiatric illness and prostatic hypertrophy or urinary retention • Amended the dose of high-dose morphine to exclude patients taking > 100 mg/day (previously stated > 120 mg/day) • Amended the criterion that stated 'Prior history of ischaemic heart disease' to 'Patients with a recent myocardial infarction (< 6 months prior to randomisation)' • Added new exclusion criteria for major amputations of the lower limbs and active diabetic foot ulcers Vital signs assessments moved from week 0 to week −2. Added guidance regarding the tapering period for morphine equivalents. Clarified that if a participant withdraws from one treatment pathway then they can start the next treatment pathway early. Clarified taper dose levels. Added information on the reporting and follow-up of pregnancy in the trial. Clarified that AEs the investigator has not been able to assess for causality will be treated as related to study medication until the causality can be fully assessed. Minor corrections and clarifications throughout the protocol. Added new sites (Birmingham and Lancashire Care) and changed PI to Solomon Tesfaye at Sheffield Teaching Hospitals
Substantial amendment 2, protocol version 4.0, approved 26 May 2017 (REC only)	Clarified that study treatment dose review is required for only severe or intolerable side effects. Updated information on emergency unblinding out of hours to allow for variation across centres. Other minor corrections and clarification throughout the protocol. New site added (Chester)
Substantial amendment 3, protocol version 5.0, approved 24 July 2017	Added serum creatinine to the list of safety blood tests. Added pregnancy test to list of assessments at randomisation and then at weeks 3, 6, 9 and 16 of each pathway for women of childbearing potential. Clarified process for emergency unblinding during office hours. Clarified methods of contraception acceptable within the trial. Removed existing site (Poole)
Substantial amendment 4, approved 18 October 2017 (REC only)	Added new sites (Bournemouth, Liverpool and Harrogate)
Substantial amendment 5, protocol version 6.0, approved 28 November 2017	Added a reduced pregabalin dosing schedule for participants with a eGFR of 30–59 ml/minute. Clarified that if a participant withdraws from the study, then any blood samples already collected would be kept unless the participant requests otherwise. Clarified the pre-screening procedures and data to be collected at the screening and randomisation visits. Added the option for participants to consent to provide daily pain scores via text message. Clarified that second-line treatment could be started up to week 13, if needed. Updated the unblinding process for safety reporting. Clarified that the blood sample for future research could be taken at the same time as any other study blood sample. Clarified the requirements for source data and the process for validating data within the Prospect database. Other minor corrections and clarifications throughout protocol

Amendment number	Summary of amendment
Substantial amendment 6, approved 15 January 2018 (REC only)	Added new sites (Aintree, Queen Elizabeth University Hospital, Edinburgh Royal Infirmary, Hairmyres Hospital, Monklands Hospital, Bradford Teaching Hospitals and New Cross Hospital)
Substantial amendment 7, protocol version 7.0, approved 13 March 2018	Clarified that assessments at weeks 1 and 7 can be completed over the telephone or via a face-to-face visit. Added details regarding the recruitment process in Scotland. Updated inclusion criteria to clarify that neuropathic pain may be present in the hands. Updated exclusion criteria: • Clarified that only non-diabetic symmetrical polyneuropathies are excluded from the trial • Clarified that only the AST/ALT results are relevant for trial eligibility • Added current history of arrhythmia to exclusion criterion 12 Updated to allow investigator discretion on the duration of the washout prior to study entry. The washout can be between 1 and 4 days, as required. Clarified that patients who are not taking any neuropathic pain medication at screening can enter straight into the baseline period. Clarified that no additional washout time is required for participants who have been tapered off opiates over a period of 2 weeks. Updated to allow participants to start study treatment on the day of randomisation or the following morning. Clarified that participant preference can be taken into account during dose titration decisions. Added Opsite patches to the list of prohibited medications. Clarified that if it was impossible to schedule a visit within the protocol-defined visit window, CTRU should be contacted for advice
Non-substantial amendment 1, approved 4 April 2018	Study medicine and pain diary updated to allow participants to start treatment on the day of randomisation or the following morning. Minor corrections made to the OPTION-DM trial leaflet and the GP letter
Substantial amendment 8, protocol v9.0, approved 11 May 2018	Updated exclusion criteria: • Exclusion criterion 7 updated to allow participants with prior concomitant and safe use of SSRIs with study medication (duloxetine and/or amitriptyline) to join the study • Exclusion criterion 21 updated to clarify that patients with active foot ulcers are eligible for the study unless the investigator feels that the ulcer would have a confounding or detrimental effect on the primary outcome or patient participation Updated to allow duloxetine to be tapered over a period of up to 2 weeks during the initial washout period, if necessary. Updated to allow the study medication to be tapered more gradually between pathways if needed at the discretion of the investigator
Substantial amendment 9, approved 21 June 2018	Updated reference safety information for amitriptyline and duloxetine
Substantial amendment 10, approved 24 July 2018	Added new sites (Derby, Gateshead and Morriston). Changed PI to Marion Devers at Monklands Hospital
Non-substantial amendment 2, approved 12 October 2018	Updated recruitment end date to February 2019
Substantial amendment 11, approved 1 November 2018	Added new sites (St Georges and Croydon)
Substantial amendment 12, protocol version 10.0, approved 8 January 2019	Updated inclusion criteria: • Inclusion criterion 3 updated to clarify that at least four questions must be answered as 'yes' on the DN4 for the patient to be eligible • Inclusion criterion 6 updated to allow patients to be randomised early if their pain scores are high, provided the mean pain score for the week is above 4

Amendment number	Summary of amendment
	Updated exclusion criteria: • Exclusion criterion 11 updated to exclude patients with heart failure class III or above (previously class II or above was excluded) • Exclusion criterion 14 updated to allow investigator discretion when excluding patients with postural hypotension (previously any patient with a postural drop of > 20 mmHg was excluded) Updated to allow a delay between screening and starting the washout/baseline weeks provided that the randomisation visit was scheduled no more than 4 weeks after screening. Clarified that both AST and ALT are required for the liver function tests. Added Ankle Brachial Pressure Index recording for patients with active foot ulcers, unless the pulse is palpable. Clarified that prescriptions must be completed by an investigator at each dispensing visit. Updated the study treatment section to clarify the treatment decisions processes. Updated to allow short-term use of prohibited medications following discussion with CTRU. Clarified that if a participant has postural hypotension at week 16 of a pathway, then the BP should be repeated at week 0 of the next pathway. Clarified that episodes of severe hypoglycaemia and diabetic ketoacidosis need to be reported as SAEs if they meet the definition of serious provided in the protocol
Non-substantial amendment 3, approved 13 March 2019	Introduced the 'end of study participant information sheet'. Updated recruitment end date to April 2019. Invitation letters updated to clarify that potential participants may be contacted by telephone. Minor changes made to the 'study medicine and pain diary' and the 'participant information sheet'
Substantial amendment 13, protocol version 11.0, approved 3 June 2019	Amended predicted sample size. Updated recruitment end date to July 2019. Updated exclusion criteria: • Exclusion criterion 7 updated to clarify that patients who are taking concomitant citalopram at study entry are not eligible • Exclusion criterion 12 updated to exclude patients with second- or third-degree heart block or left bundle branch block (patients with right bundle branch block or first-degree heart block may be included following discussion with the cardiology team)
Substantial amendment 14, approved 26 September 2019	Genetic analysis substudy protocol submitted for approval
Substantial amendment 15, approved 22 September 2020	End-of-trial definition updated to allow sample analyses to be completed. The end of trial is now defined as the completion of all sample analyses

BP, blood pressure; REC, Research Ethics Committee.

Appendix 4 Subgroup analyses

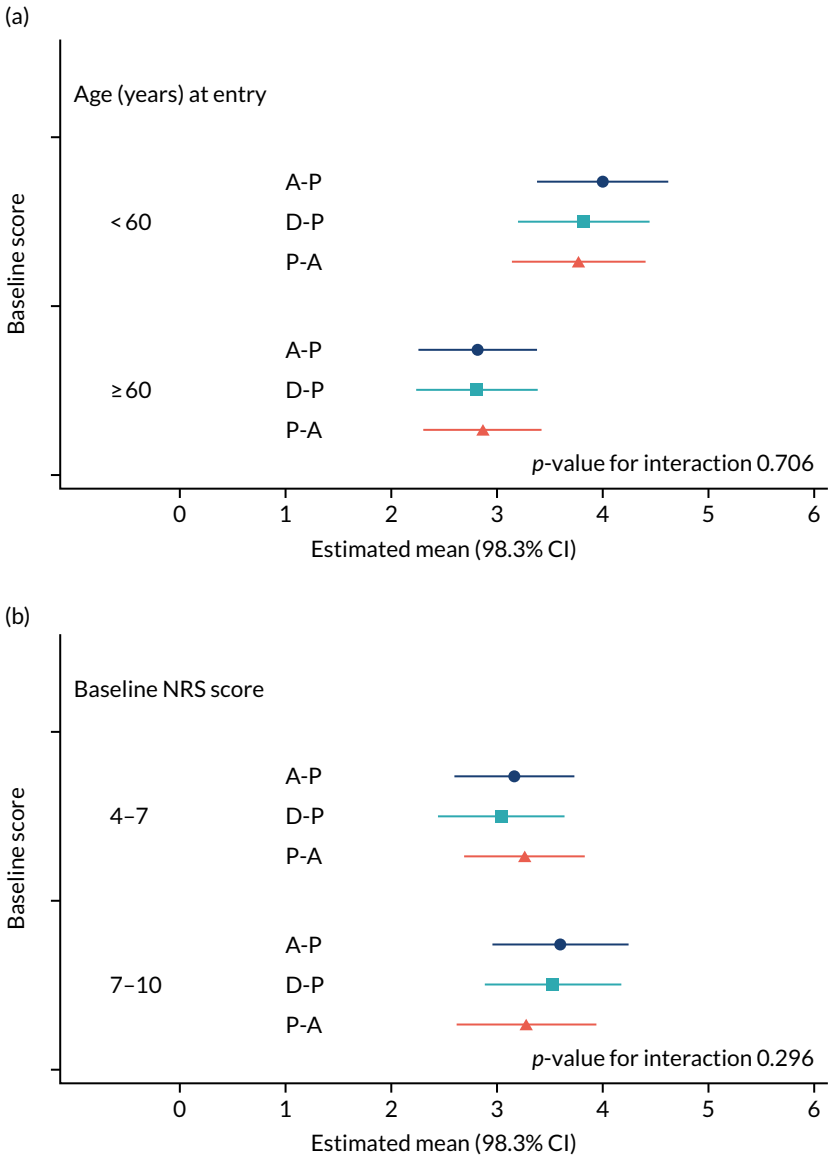
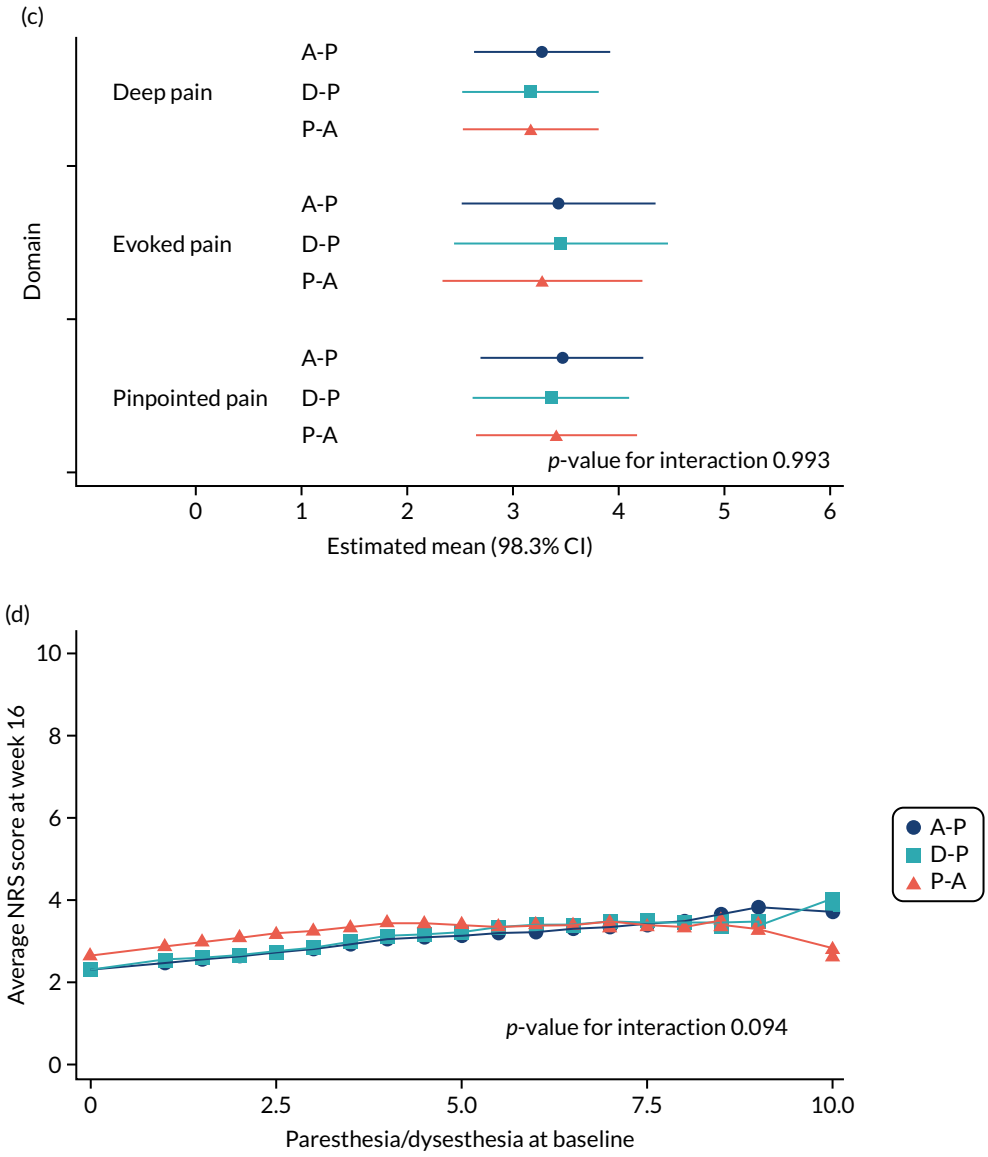


FIGURE 16 Numeric Rating Scale pain at week 16 by subgroup. (a) NRS by age subgroup (values are least square means ± 98.3% CI); (b) NRS by pain at baseline (values are least square means ± 98.3% CI); (c) NRS by NPSI pain phenotype – overall classification[52] (values are least square means ± 98.3% CI); (d) NRS by baseline NPSI paraesthesia/dysaesthesia pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (e) NRS by baseline NPSI evoked pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (f) NRS by baseline NPSI paroxysmal pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (g) NRS by baseline NPSI deep spontaneous/pressing pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (h) NRS by baseline NPSI superficial spontaneous/burning pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (i) NRS by NPSI pain phenotype – total pain score (values are derived from lowess plot of response in relation to baseline NPSI score); (j) NRS by HADS anxiety (values are derived from lowess plot of response in relation to baseline HADS score); (k) NRS by HADS depression (values are derived from lowess plot of response in relation to baseline HADS score); (l) NRS by previous use of amitriptyline (values are least square means ± 98.3% CI); (m) NRS by previous use of duloxetine (values are least square means ± 98.3% CI); (n) NRS by previous use of pregabalin (values are least square means ± 98.3% CI); (o) NRS by previous use of opioids (values are least square means ± 98.3% CI); (p) longitudinal NRS by time [values are derived from lowess plot of the residuals for response in a longitudinal model in which the covariates are treatment, period and week of pathway (0–16); residual standardised for treatment pathway, pathway week and treatment group]; and (q) NRS by pre-/post-lockdown (values are least square means ± 98.3% CI). (*continued*)



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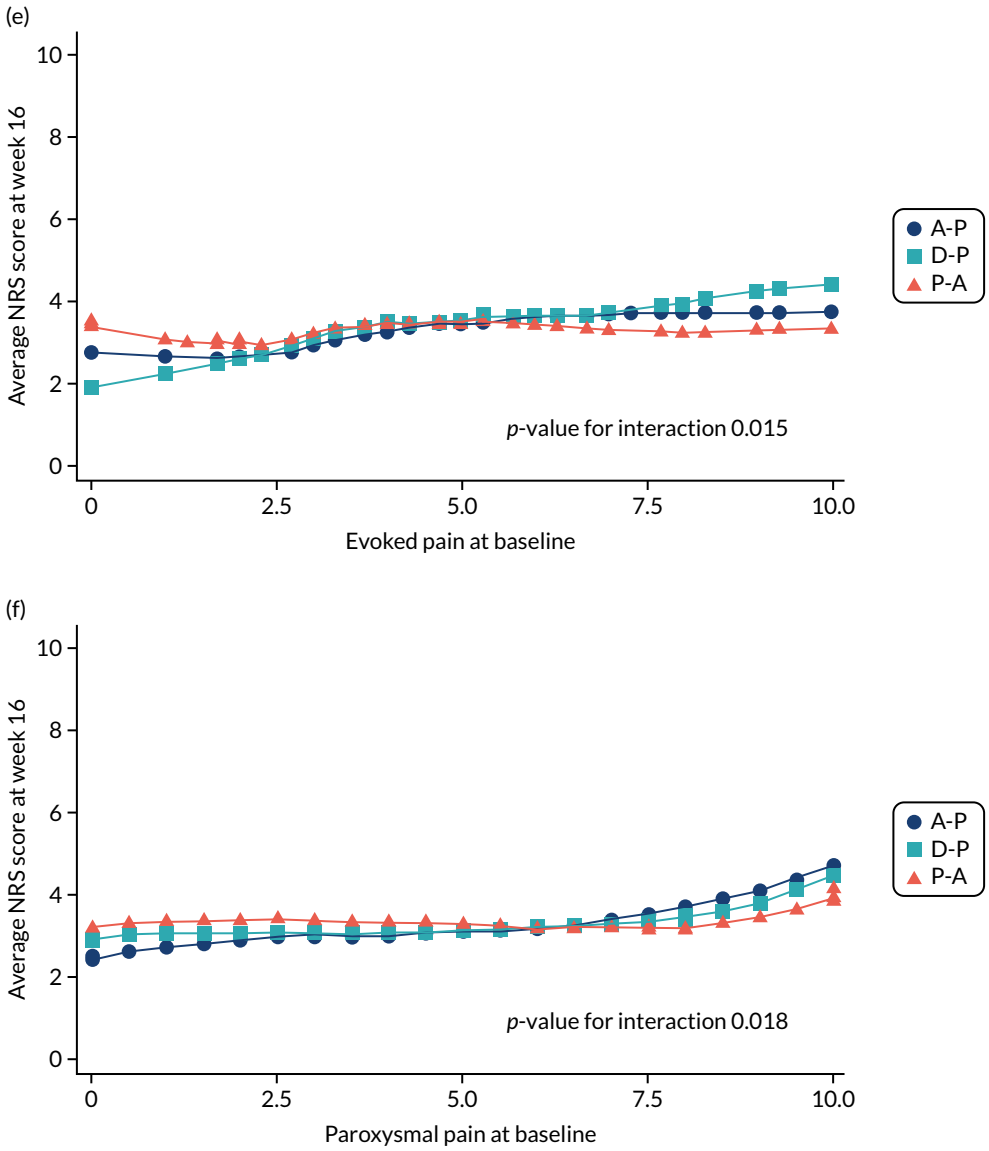

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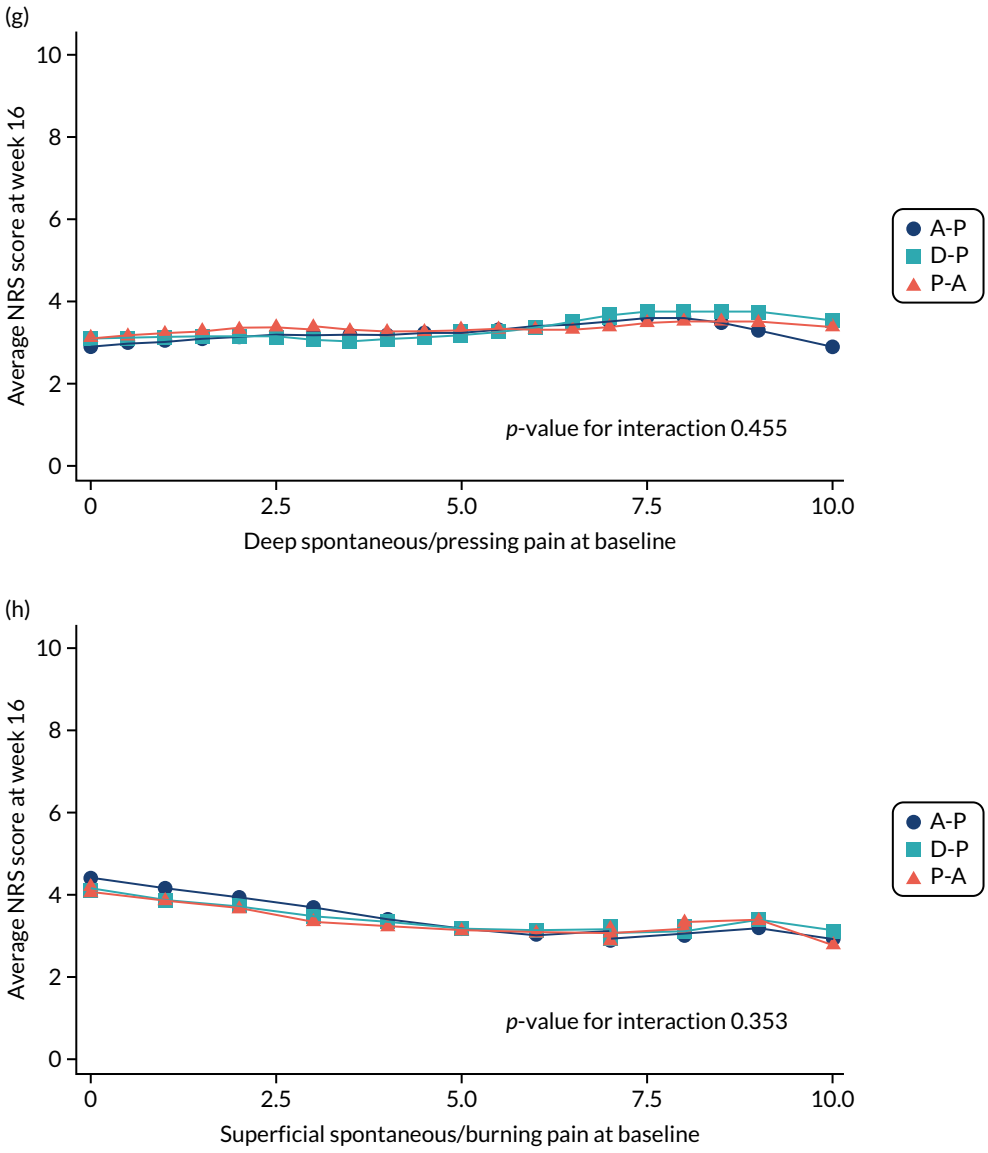

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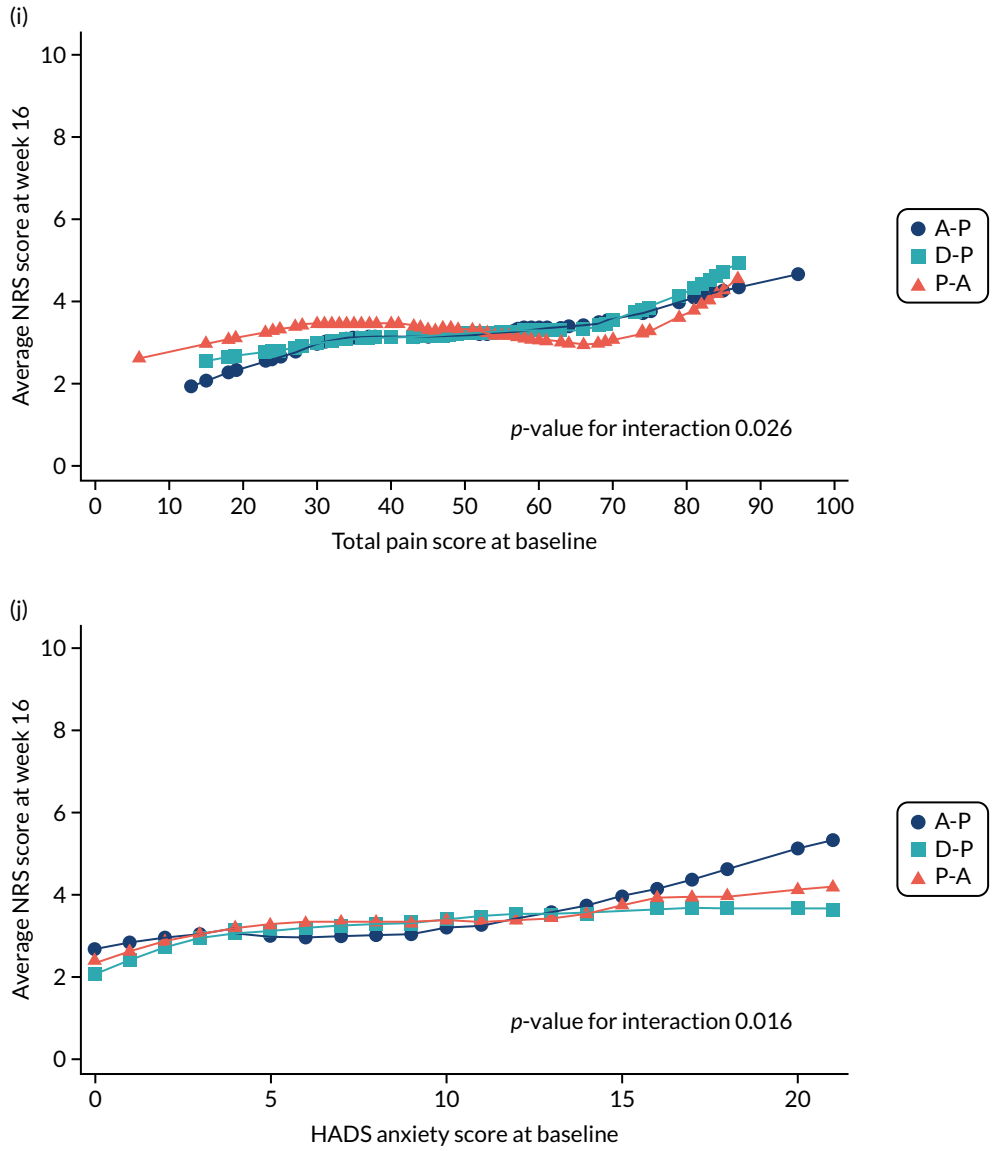

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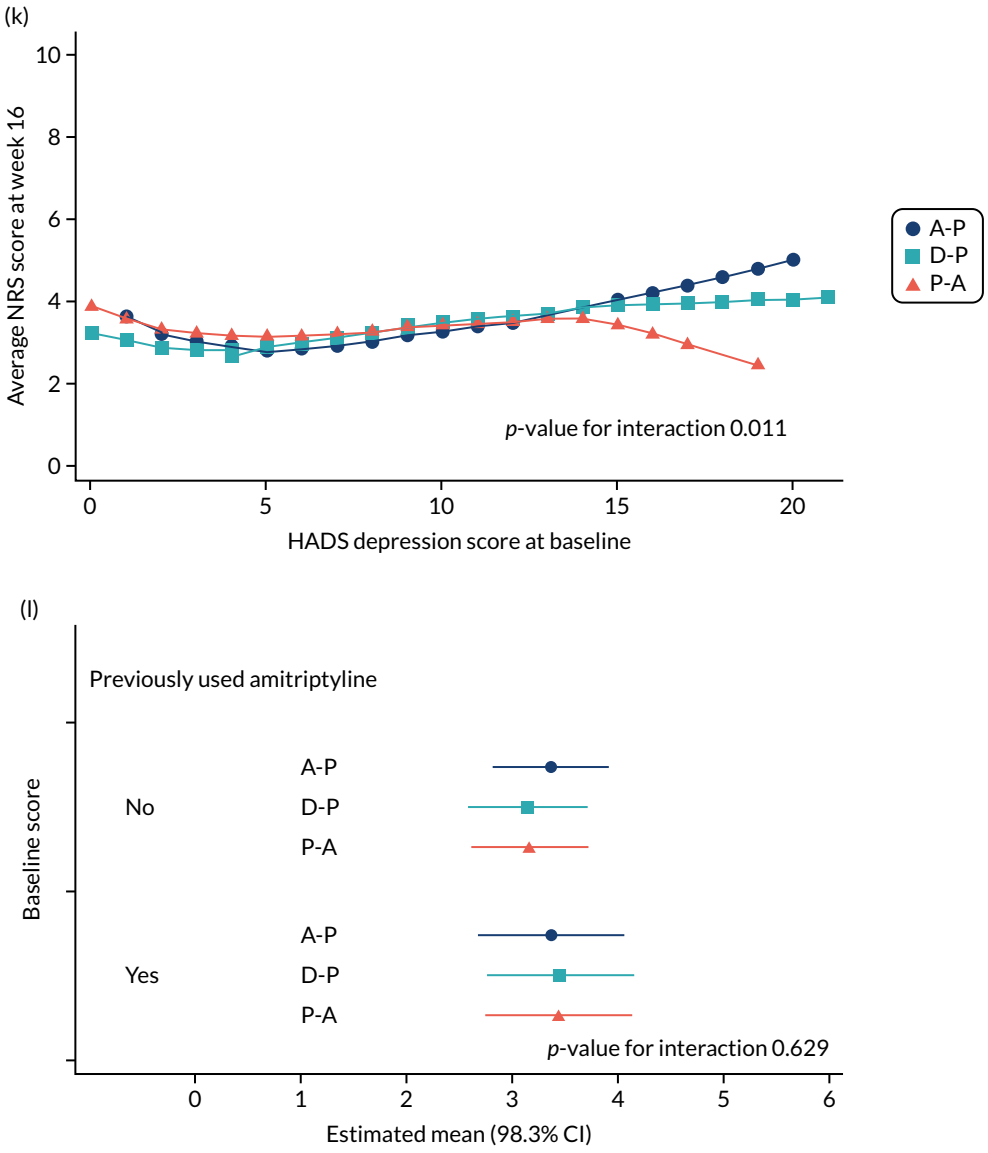

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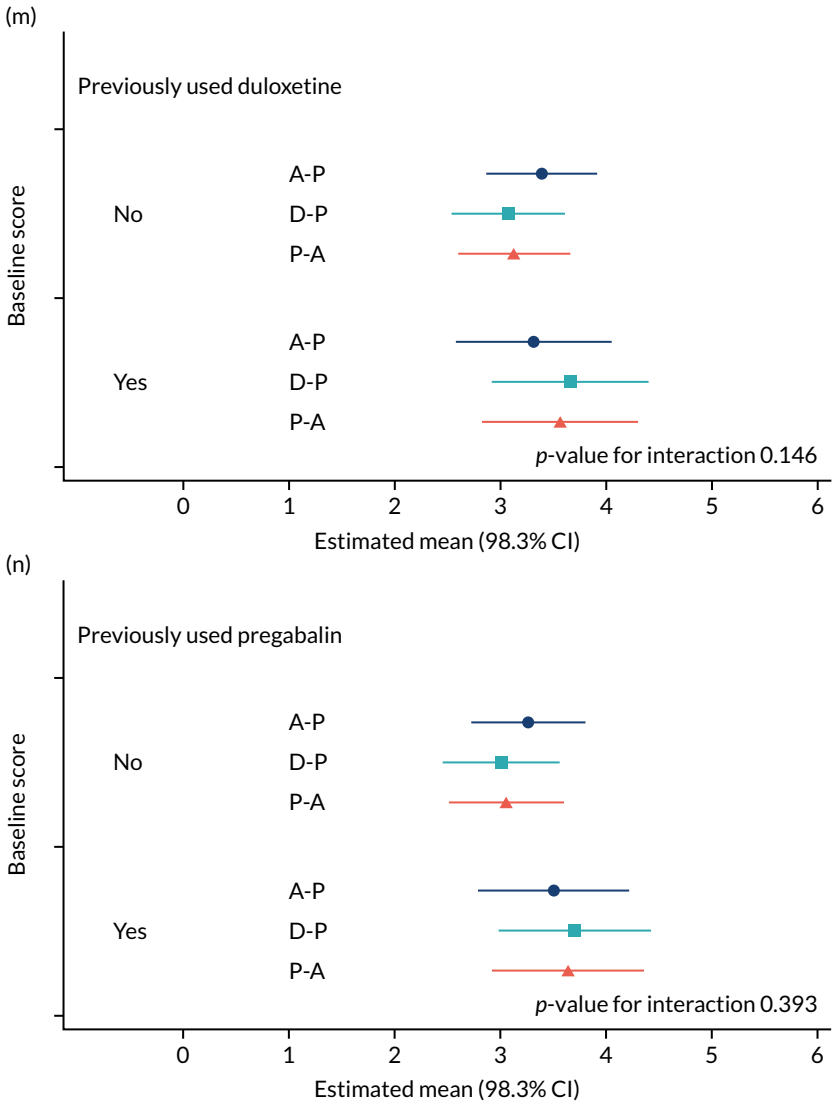

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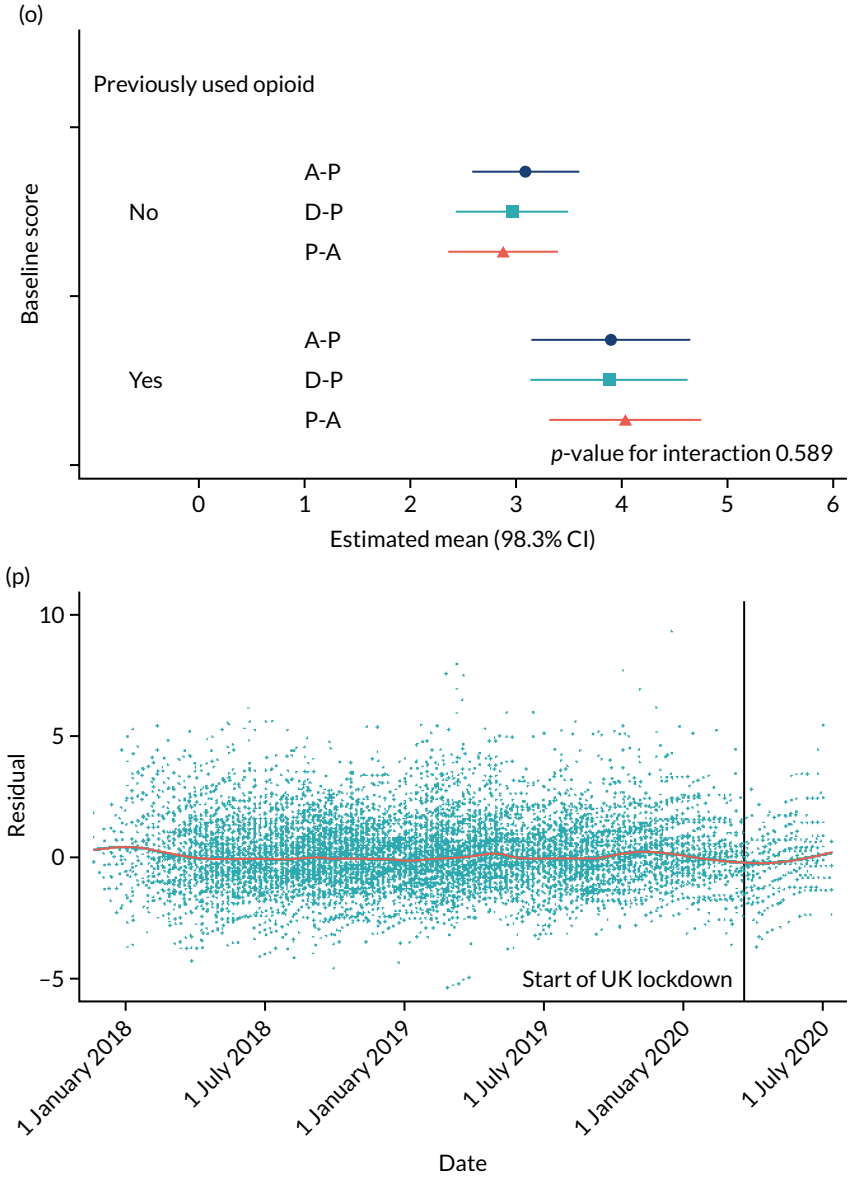

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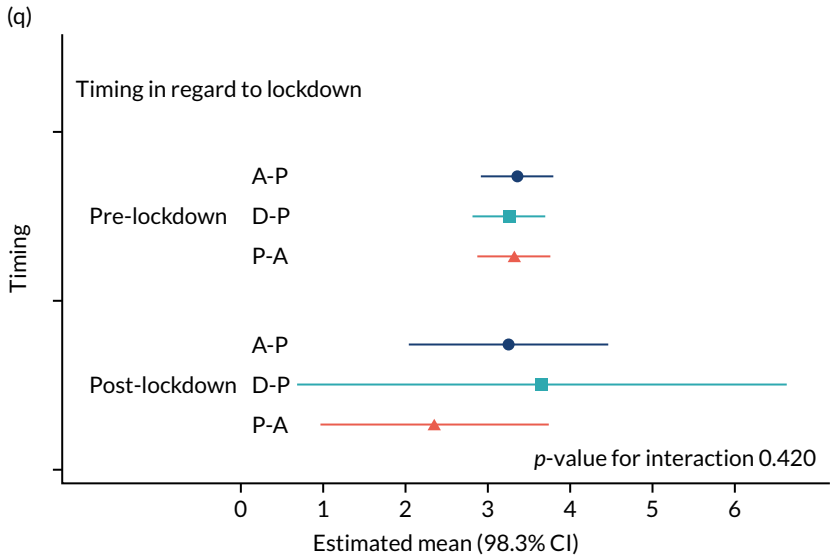

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Appendix 5 Concomitant medications

	Treatment pathway		
Medication	**A-P**	**D-P**	**P-A**
Insulin	10	16	13
Canagliflozin	2	0	1
Dapagliflozin	3	5	0
Dulaglutide (Trulicit)	1	5	3
Empagliflozin	6	4	4
Exenatide (Bydureon)	0	1	0
Gliclazide	12	10	13
Linagliptin	2	2	3
Liraglutide	5	3	4
Metformin	27	29	25
Pioglitazone	1	3	1
Saxagliptin	0	1	0
Sitagliptin	2	0	6
Amlodipine	13	11	8
Atenolol	3	4	1
Bendroflumethiazide	2	5	4
Furosemide	3	2	3
Lansoprazole	7	9	8
Omeprazole	8	7	9
Ramipril	14	14	9
Simvastatin	13	11	7
Total	134	142	122

EME
HSDR
HTA
PGfAR
PHR

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