META-ANÁLISIS: ALTERNATIVAS TERAPEÚTICAS EN EL TRATAMIENTO DEL DOLOR NEUROPÁTICO EN EL PIE DIABÉTICO

TESIS DOCTORAL

Samuel Vilar Palomo

META-ANÁLISIS: ALTERNATIVAS TERAPÉUTICAS EN EL TRATAMIENTO DEL DOLOR NEUROPÁTICO EN EL PIE DIABÉTICO

Doctorado Interuniversitario en Ciencias de la Salud

Departamento de Podología

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HACEN CONSTAR:

Que D. SAMUEL VILAR PALOMO ha realizado, bajo su dirección y coordinación, este trabajo original de investigación titulado: **"Meta-análisis: Alternativas terapéuticas en el tratamiento del dolor neuropático en el pie diabético"**, para optar al grado de Doctor por la Universidad de Sevilla, y que dicho trabajo reúne las condiciones necesarias para ser sometido a lectura y defensa ante el tribunal.

Sevilla a 15 de mayo de dos mil diecinueve.

Los Directores,

Fdo. Dra. María Reina Bueno   Fdo. Dr. Pedro V. Munuera Martínez

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D. **Samuel Vilar Palomo**, Diplomado en Enfermería y Diplomado en Podología

HACE CONSTAR:

Que ha realizado la tesis doctoral denominada "**Meta-análisis: Alternativas terapéuticas en el tratamiento del dolor neuropático en el pie diabético**", matriculado en el Programa Interuniversitario de Doctorado en Ciencias de la Salud por las Universidades de Sevilla y Jaén, en la línea de investigación "Procedimientos, intervenciones y resultados en salud", bajo la dirección de los doctores Dª. María Reina Bueno y D. Pedro V. Munuera Martínez, y la tutorización del doctor D. José Manuel Castillo López.

Y para que conste y surta los efectos oportunos, se firma en Sevilla, a 15 de mayo de 2019.

El doctorando,

Fdo. Samuel Vilar Palomo

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RESUMEN

Objetivos

Evaluar la eficacia en el alivio del dolor de las alternativas terapéuticas existentes para el tratamiento de la neuropatía diabética dolorosa

Metodología

Se realizó una búsqueda en las principales bases de datos para Ciencias de la Salud como son PUBMED y Web of Science (WOS) para obtener ensayos clínicos aleatorizados con grupo control sobre tratamientos utilizados para la neuropatía diabética dolorosa. Los estudios analizados debían de cumplir con los criterios de inclusión y exclusión seleccionados, considerando especialmente los resultados relacionados con la intensidad del dolor, además de cumplir los criterios de calidad mediante escala JADAD. Tras la selección de los estudios se realizó una evaluación del nivel de riesgo de los estudios incluidos y se procedió a la extracción de datos de los estudios incluidos para posteriormente realizar el meta-análisis de los mismos.

Resultados

Se obtuvieron 12 ensayos clínicos aleatorizados sobre tratamientos farmacológicos orales, físicos y tópicos para la neuropatía diabética dolorosa, con un total de 2872 pacientes incluidos. A través del meta-análisis realizado se obtuvo el estadístico g de Hedges para los estudios de Richter 2005 (Pregabalina 150 mg/día (g: 0,407; 0,070 a 0,744; p<0,05), Pregabalina 600 mg/día(g: 0,607; 0,235 a 0,980; p<0,05)), Raskin 2005 (Duloxetina 60 mg/día (g: 4,984; 4,961 a 5,007; p<0,05), Duloxetina 120 mg/día (g: 3,710; 3,687 a 3,733; p<0,05)), Goldstein 2004 (Duloxetina 20 mg/día (g: 1,622; 1,594 a 1,650; p<0,05), Duloxetina 60 mg/día (g: 3,534; 3,505 a 3,562; p<0,05), Duloxetina 120 mg/día (g: 5,448; 5,419 a 5,477; p<0,05)), Wernicke 2006 (Duloxetina 60 mg/día (g: 5,007; 4,977 a 5,036; p<0,05), Duloxetina 120 mg/día (g: 4,983; 4,952 a 5,013; p<0,05)), Niesters 2013 (Tapentadol 500 mg/día (g: 1,333; 1,072 a 1,594; p<0,05)) y Eisenberg 2001 (Lamotrigina 400 mg/día (g: 10,837; 10,811 a 10,864; p<0,05)). Para el resto de

estudios no se obtuvo efecto positivo por valor de p>0,05. Los resultados obtenidos también se muestran mediante gráfica tipo Forest Plot.

Conclusiones

Según los resultados obtenidos las terapias más efectivas para el tratamiento de la neuropatía diabética dolorosa son la duloxetina, pregabalina, tapentadol y lamotrigina. Sin embargo, en cuanto a términos de eficacia y aplicabilidad clínica, las terapias farmacológicas orales sobre duloxetina, pregabalina y gabapentina estarían consideradas como primera línea de recomendación, siendo el tapentadol u otros opioides la segunda línea de recomendación , y la capsaicina tópica la terapia adyuvante en caso de no ser posible la ingesta oral de fármacos.

SUMMARY

Objectives

To assess the efficacy in pain relief of existing therapeutic alternatives for the treatment of painful diabetic neuropathy.

Methodology

A search was made in the main databases for Health Sciences such as PUBMED and Web of Science (WOS) to obtain randomized clinical trials with a control group on treatments used for painful diabetic neuropathy. The studies analyzed must meet the inclusion and exclusion criteria selected, especially considering the results related to the intensity of pain, in addition to meeting the quality criteria using the JADAD scale. After the selection of the studies, an assessment of the risk level of the included studies was carried out and the data were extracted from the included studies to later perform the meta-analysis of the same.

Results

We obtained 12 randomized clinical trials on oral, physical and topical pharmacological treatments for painful diabetic neuropathy, with a total of 2872 patients included. Through the meta-analysis performed, the Hedges g statistic was obtained for the following studies: Richter 2005 (Pregabalin 150 mg / day (g: 0.407, 0.070 to 0.744, p <0.05), Pregabalin 600 mg / day (g: 0.607, 0.235 to 0.980, p <0.05), Raskin 2005 (Duloxetine 60 mg / day (g: 4.984, 4.961 to 5.007, p <0.05), Duloxetine 120 mg / day (g: 3.710, 3.687 a 3,733, p <0.05), Goldstein 2004 (Duloxetine 20 mg / day (g: 1.622, 1.594 to 1.650, p <0.05), Duloxetine 60 mg / day (g: 3.534, 3.505 to 3.562, p < 0.05), Duloxetine 120 mg / day (g: 5.448, 5.419 to 5.477, p <0.05)), Wernicke 2006 (Duloxetine 60 mg / day (g: 5.007, 4.977 to 5.036, p <0.05) , Duloxetine 120 mg / day (g: 4.983, 4.952 to 5.013, p <0.05)), Niesters 2013 (Tapentadol 500 mg / day (g: 1.333, 1.072 to 1.594, p <0.05)) and Eisenberg 2001 (Lamotrigine 400 mg / day (g: 10.837, 10.811 to 10.864, p <0.05)). For the rest of the studies, no positive effect was obtained for p value> 0.05. The results obtained are also shown by Forest Plot graph.

Conclusions

According to the results obtained, the most effective therapies for the treatment of painful diabetic neuropathy are duloxetine, pregabalin, tapentadol and lamotrigine. However, regarding terms of efficacy and clinical applicability, oral pharmacological therapies on duloxetine, pregabalin and gabapentin would be considered as the first line of recommendation, being tapentadol or other opioids the second line of recommendation, and topical capsaicin adjuvant therapy if oral intake of drugs is not possible.

INTRODUCCIÓN

Problema de investigación

La Diabetes Mellitus (en adelante DM) es una enfermedad que afecta a 425 millones de personas en el mundo, estimándose para el año 2045 una prevalencia de 629 millones de personas afectadas por esta enfermedad, siendo la neuropatía diabética una de sus complicaciones más importantes junto con las enfermedades cardiovasculares. Las cifras son mas preocupantes al saber que en 2017 se estima que las muertes relacionadas con la DM se sitúan en torno a los 4 millones de personas. (1,2).

La neuropatía diabética se define como la presencia de síntomas o signos de disfunción del sistema nervioso periférico en el paciente diabético (3). Ésta complicación de la DM se caracteriza por una presentación mas común denominada polineuropatía simétrica distal, cuyas manifestaciones principales son la presencia de una distribución muy característica denominada en guante y calcetín, donde hay una afectación de fibras nerviosas que alteran la sensación térmica y dolorosa y la sensibilidad vibratoria y propioceptiva. A su vez, las manifestaciones clínicas de esta patología de caracterizan por la aparición predominantemente nocturna de parestesias o entumecimiento, dolor quemante, alodinia, disestesias o escozor, apareciendo a su vez edemas, atrofia y debilidad muscular, disminución de reflejos osteotendinosos y pérdida de sensibilidad cuando la enfermedad continua su progresión (4–7).

Como ya se ha comentado anteriormente, una de las características de la neuropatía diabética es la presencia de dolor, en cuyo caso se denomina neuropatía diabética dolorosa (en adelante NDD), que es definida por la *Asociación Internacional para el estudio del Dolor* como el dolor que surge como consecuencia directa de anomalías en el sistema somatosensorial en personas con DM (8). Éste proceso doloroso puede conllevar alteraciones en el plano psicológico y afectivo, además de incapacidades y deterioro en la calidad de vida de los pacientes (9–11).

Ante las importantes consecuencias de la neuropatía diabética dolorosa, existen diferentes tratamientos cuya función principal es intentar reducir el nivel de dolor que sufren estos pacientes (12–16). El arsenal terapéutico existente para el tratamiento de la NDD puede dividirse en 3 grupos claramente diferenciados:

- Terapias farmacológicas orales, entre las que se encuentran los grupos farmacológicos denominados antidepresivos, antiepilépticos y opioides fundamentalmente. Un ejemplo de estos fármacos serían la gabapentina, pregabalina, duloxetina, tapentadol, o topiramato entre otros.
- Terapias tópicas, cuyos principales agentes terapéuticos consisten en la aplicación de capsaicina tópica, clonidina, ketamina, entre otros.
- Terapias físicas, las cuales se basan en terapias eléctricas o electromagnéticas, como son las terapias mediante TENS, FREMS, PENS magnetoterapia o neuroestimulación entre otros.

Todas estas terapias componen un grupo de tratamientos en manos de los profesionales de la salud con el que conseguir que los pacientes alivien el dolor producido por la NDD y mejoren su calidad de vida.

Justificación y pertinencia

En la literatura científica existen diversas revisiones de importancia realizadas sobre los tratamientos para la NDD, cuyos resultados en gran mayoría coinciden, y son de gran utilidad a la hora de abordar dicha patología. Sin embargo, muchos de los artículos relacionados con el tratamiento de la NDD no cumplen criterios de calidad metodológica, y algunos de ellos son incluidos en las revisiones mencionadas anteriormente. A ello se une que gran parte de dichas revisiones tienen cierta antigüedad, y existen ensayos clínicos realizados posteriormente a las mismas, por lo que se hace más necesario aún la realización de revisiones más actualizadas con cierta calidad metodología en los estudios que se incluyan.

Los avances continuos en la investigación del manejo del dolor neuropático y la aparición de mayor cantidad de terapias diferentes y estudios más actualizados hacen necesario que los profesionales de Podología y resto de disciplinas relacionadas con la salud actualicen constantemente los conocimientos acerca de esta patología y sus tratamientos.

En el caso del profesional de la Podología es mas importante si cabe debido a sus competencias en el abordaje de pacientes con DM y problemas en los pies, lo que conlleva a su vez estar capacitados para actuar ante las complicaciones del mismo, como es el caso de la neuropatía diabética y la aparición de dolor. A esto se le une que la presencia de pacientes con pie diabético es cada vez más frecuente en las consultas de Podología, siendo mas necesario si cabe la continua actualización de conocimientos en torno a la NDD.

Debido a todo ello es por lo que se hace necesario la realización de este estudio, a través del cual se pretende obtener unos resultados actualizados sobre los tratamientos para la NDD que nos ayuden en la toma de decisiones para el correcto abordaje clínico de estos pacientes con el fin de aliviar el dolor que padecen.

MARCO TEÓRICO

Diabetes Mellitus

La Diabetes Mellitus es un desorden metabólico caracterizado por la presencia de hiperglucemia debida a una deficiente secreción de insulina, deficiente acción de la misma, o ambos (2). Esta hiperglucemia mantenida puede provocar daños orgánicos de relevante importancia por la presencia de enfermedades renales, oculares, cardiovasculares y neuropatías entre otros. La DM se clasifica en DM Tipo 1, DM Tipo 2 y DM gestacional (1). La DM Tipo I se produce por la insuficiente o nula producción de insulina a través del páncreas, siendo la DM Tipo II generada por una inadecuada producción de esta hormona y la incapacidad del organismo a reaccionar a ella (1). Se habla de DM gestacional cuando existe una primera cifra elevada de glucosa en sangre durante el proceso del embarazo (1).

Según la Federación Internacional de Diabetes (en adelante FID) en su octava y última edición de 2017 (1), la DM afecta a nivel mundial a 425 millones de personas, 327 millones correspondientes a personas de edad comprendida entre 20 – 64 años, y 98 millones a edades superiores a 65 años. Se estima que para el año 2045 estas cifras aumenten a un total de 629 millones de personas, 438 de ellas correspondientes a la horquilla de edad 20 – 64 años y 191 a 65 años en adelante. Estas cifras son de suma importancia sabiendo además que las muertes relacionadas con DM rondan los 4 millones de personas en 2017 (1).

En cuanto a los datos a nivel europeo, los afectados por DM en 2017 se sitúan en 58 millones de personas, estimándose para 2045 en 67 millones. Otro aspecto importante relacionado con la DM es su existencia sin diagnosticar, por lo que se cree que existen 22 millones de personas en Europa en esta situación. A nivel nacional, los datos sobre DM nos colocan en una prevalencia en torno al 10,4 %, con la importante cifra de 11.557,2 muertes relacionadas con esta enfermedad. Otro aspecto importante a destacar es la prevalencia de la enfermedad en los

pacientes varones hasta los 70 años, siendo más prevalente en mujeres a partir de esa edad (1).

Los datos obtenidos por la FID reflejan una situación preocupante en cuanto a la prevalencia y mortalidad de la DM y sobre todo a las enfermedades que se relacionan con su existencia, las cuales pueden conllevar un serio deterioro de la vida del paciente. En este aspecto, dos de los problemas derivados de la DM que más nos preocupan son las enfermedades cardiovasculares y la neuropatía diabética (1).

Con respecto al grupo de <u>enfermedades cardiovasculares</u>, la enfermedad arterial periférica resulta de gran importancia para el tema que tratamos debido a su importante implicación en la aparición del pie diabético, como veremos a continuación (17).

- **Enfermedad arterial periférica**

La enfermedad arterial periférica es definida como un proceso clínico en el que se produce una oclusión o estenosis de trayectos arteriales, de miembros inferiores predominantemente, debido a un proceso ateroesclerótico (18,19). Esta ateroesclerosis es el resultado de un proceso por el que factores de riesgo producen fundamentalmente un acúmulo de lipoproteínas de baja densidad (LDL) en la capa túnica íntima de las arterias debido a un daño endovascular, siendo éstos oxidados por radicales libres generados en macrófagos, células endoteliales y células de músculo liso. Este proceso conlleva una respuesta del sistema inmune e inflamación que favorece a su vez el depósito de LDL en la pared arterial y un engrosamiento de la capa túnica íntima, creándose así un círculo vicioso donde se produce una reducción del espacio intravascular y la aparición de una placa de ateroma. En el caso de la DM, este proceso de formación ateroesclerótica se ve acelerado por la hiperglucemia mantenida fundamentalmente (20,21).

La ateroesclerosis en la principal causa de enfermedad arterial periférica en personas mayores de 40 años, aumentando el riesgo de sufrirla aún más en

pacientes con DM. Se estima que en esa población el riesgo de padecer esta enfermedad es de 9,5 % en personas con DM frente al 4,5 % en personas sin DM (19).

- **Neuropatía diabética**

La otra afección de suma importancia que puede aparecer en los pacientes con DM es la neuropatía diabética, definiéndose como la presencia de síntomas o signos de disfunción del sistema nervioso periférico en el paciente con DM (3), una vez excluidas otras causas, ya que como se demostró en el estudio de Rochester en 1993 alrededor del 10% de las neuropatías que se diagnosticaban como diabéticas no lo eran en realidad, sino que tenían una etiología diferente a la DM. Este mismo estudio apuntaba que aproximadamente entre el 60 – 70% de los pacientes con DM presentan algún tipo de neuropatía (22). La patogenia de la neuropatía diabética no se conoce con exactitud, existiendo varias teorías que relacionan su desarrollo a factores metabólicos, factores vasculares o trastornos en mecanismos de reparación y mantenimiento de fibras nerviosas periféricas (6).

En la actualidad se considera la neuropatía periférica diabética como una de las complicaciones más frecuentes de la DM (7,23). La prevalencia a nivel nacional de esta afección se sitúa entre el 13% y 24% en pacientes con DM tipo 1 y DM tipo 2 respectivamente (7). Dentro de la neuropatía diabética periférica, la forma mas común de presentación es la polineuropatía simétrica distal (Figura 1) (24,25).
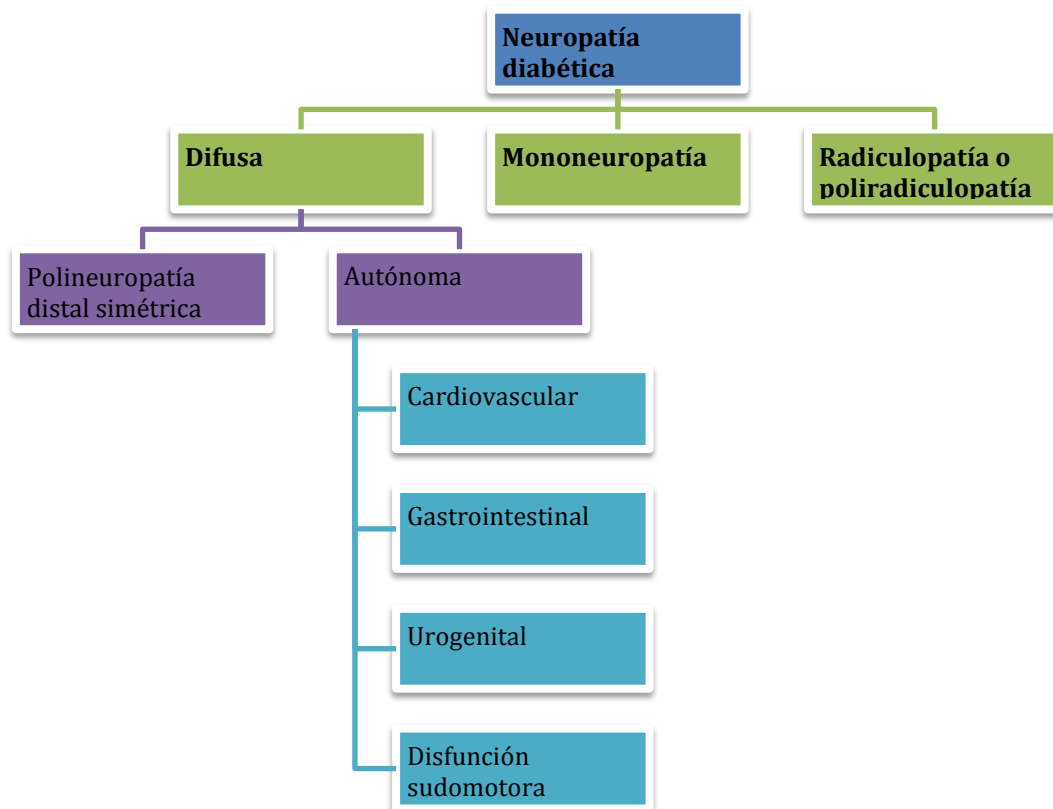
Figura 1: Tipos de neuropatía diabética (7)

La polineuropatía simétrica distal se caracteriza por una distribución denominada en guante y calcetín. Afecta en su inicio a las fibras nerviosas más pequeñas sin recubrimiento de mielina y que conducen la sensación térmica y dolorosa, seguido por la afectación de las fibras nerviosas más largas con recubrimiento de mielina que se encargan de la sensibilidad vibratoria y propioceptiva. Su evolución va de distal a proximal, siendo la afectación en los pies la mayoritaria, y la afectación en manos la minoritaria y tardía. La prevalencia de este tipo de presentación se sitúa en torno al 50 % en personas DM tipo 2 mayores de 60 años. Los síntomas iniciales que suelen tener los pacientes van relacionados con la presencia de parestesias o entumecimiento, pudiendo aparecer también dolor quemante, alodinia, disestesias o escozor, todos ellos de predominio nocturno. Cuando la enfermedad va avanzando pueden aparecer edemas, atrofia y debilidad muscular, disminución de reflejos osteotendinosos y pérdida de sensibilidad. Todos estos síntomas pueden conllevar la aparición de procesos ulcerosos y la artropatía de Charcot (4–7).

La presencia de estas dos patologías analizadas anteriormente puede conllevar una de las complicaciones mas determinantes en un paciente diabético, el denominado pie diabético.

- **Pie diabético**

Para la Organización Mundial de la Salud (en adelante OMS) el pie diabético consiste en la "*presencia de ulceración, infección y/o gangrena del pie asociada a la neuropatía diabética y diferentes grados de enfermedad vascular periférica, resultados de la interacción compleja de diferentes factores inducidos por una hiperglicemia mantenida*" (26).

Se estima una prevalencia del pie diabético a nivel mundial que va del 3 % al 13 %, con un promedio del 6,4 %, estimándose también que entre el 15 % y 25 % de personas diabéticas sufrirán a lo largo de su vida un proceso ulceroso que puede conllevar la amputación del miembro (27).

Según el Consenso sobre Úlceras Vasculares y Pie Diabético de la Asociación Española de Enfermería Vascular y Heridas (en adelante AEEVH) existen 3 tipos de factores que componen el síndrome del pie diabético (28):

☐ Factores predisponentes: Neuropatía asociada en mayor o menor grado a una macro o microangiopatía.

☐ Factores desencadenantes: Traumatismos mecánicos, térmicos o químicos.

☐ Factores agravantes: Nos determinarán el pronóstico de la enfermedad, como la infección, la isquemia y la neuropatía.

- **Neuropatía diabética dolorosa**

Una vez analizado el síndrome del pie diabético y las patologías más importantes que lo componen, esta tesis pondrá el foco sobre uno de los síntomas más importantes derivados de la DM como es el **dolor neuropático o también**

denominado neuropatía diabética dolorosa, definida por la *Asociación Internacional para el estudio del Dolor* (en adelante IASP) como el dolor que surge como consecuencia directa de anomalías en el sistema somatosensorial en personas con DM (8). Este tipo de dolor tiene los principales signos y síntomas mostrados en la tabla 1 (29).

Signos/síntomas dolor neuropático	Signos/síntomas neuropatía diabética dolorosa
Dolor urente espontáneo	Dolor urente espontáneo
Dolor disestésico espontáneo	Dolor disestésico espontáneo
Dolor espontáneo profundo opresivo	
Dolor espontaneo de otras cualidades	Dolor espontáneo de otras cualidades
Alodinia mecánica dinámica	
Alodinia mecánica estática	
Alodinia al calor	
Alodinia al frio	
Hiperalgesia mecánica	
Hiperalgesia al calor	Hiperalgesia al calor
Hiperalgesia al frío	Hiperalgesia al frío
Disestesias provocados por tacto	Disestesias provocados por tacto
Parestesias provocadas por tacto	Parestesias provocadas por tacto
Signo de Tinel que induce a hormigueos	
Signo de Tinel que induce dolor urente	
Dolor referido	
Distorsión de la cualidad de la sensación	

Localización errónea de las sensaciones	
Patrones anormales de sumación temporal	

Tabla 1: Signos y síntomas relacionados con dolor neuropático y neuropatíaa diabética dolorosa (29)

Esta complicación derivada de la DM genera un importante deterioro de la calidad de vida y altos grados de invalidez. Se estima que un 20 % de los pacientes con polineuropatía simétrica distal sufren dolor (10). A la repercusiónn fisiológica derivada de esta enfermedad se le une el aspecto psíquico o afectivo-emocional que también se ve afectado en estos pacientes. La combinación de todos estos factores genera un estado continuo de malestar y ansiedad en ellos que terminan por complicar la resoluciónn del problema (9,11).

La NDD se trata mediante numerosas alternativas terapéuticas. Las formas más comunes de tratamiento son los fármacos antidepresivos, anticonvulsionantes, opioides y anestésicos locales entre otros, cuyo uso está avalado mediante diversos estudios por parte sociedades internacionales, revisiones Cochrane y guías de práctica clínica. Además de estos fármacos, la mayoría administrados por vía oral, existen otras formas de presentación también utilizadas comúnmente como parches o cremas, así como tratamientos no farmacológicos como son las denominadas terapias físicas, entre las que se destacan la magnetoterapia, la estimulación nerviosa transcutánea o la estimulación medular.

Terapias utilizadas en el tratamiento del dolor neuropático

El tratamiento del dolor neuropático se basa fundamentalmente en el control de los signos y síntomas derivados de éste. Existen diversas opciones de tratamiento para los pacientes que sufren este tipo de dolor, pudiéndose englobar en dos grupos bien determinados: los tratamientos farmacológicos (orales y tópicos) y las terapias físicas.

Componen un grupo de fármacos de diversas características pudiéndose clasificar según el tipo de fármaco (Tabla 2). Cabe destacar que el uso de analgesia de primer escalón (véase fármacos no opioides tales como paracetamol, nolotil, antiinflamatorios, entre otros) no es de elección para esta patología por su ineficacia.

TRATAMIENTO FARMACOLÓGICO	
TIPOS	**EJEMPLOS**
Antidepresivos	Amitriptilina, Duloxetina, Venlafaxina, Paroxetina…
Antiepilépticos	Gabapentina, Pregabalina, Oxcarbacepina, Topiramato…
Opioides	Tramadol, Oxicodona, Morfina, Fentanilo…
Tratamientos tópicos	Parche de Capsaicina 8%, Parche de Lidocaína 5%…

Tabla 2: Tipos de fármacos usados para el tratamiento del dolor neuropático (13,30)

1. *Fármacos antidepresivos.*

Se trata de un grupo de fármacos de gran importancia por el habitual uso y efectividad en el tratamiento del dolor neuropático, aún no siendo su indicación primaria. El mecanismo de acción de estos fármacos para el alivio del dolor todavía sigue siendo algo relativamente desconocido. El alivio del dolor se consigue normalmente de manera rápida (pocos días) y a bajas dosis (31). Dentro de este grupo de fármacos nos podemos encontrar varios tipos:

- Antidepresivos tricíclicos (TCA): Amitriptilina, Imipramina
- Inhibidores selectivos de la recaptación de serotonina (ISRS): Paroxetina
- Inhibidores de la recaptación de serotonina y noradrenalina (IRSN): Duloxetina, Venlafaxina

La dosis máximas diarias de estos fármacos van desde los 60-120 mg para la duloxetina, los 150-225 mg para la venlafaxina y los 25-150 mg para el resto de antidepresivos tricíclicos (30–32).

2. *Fármacos antiepilépticos*

Los fármacos antiepilépticos constituyen el otro grupo de más importancia para el tratamiento del dolor neuropático. El mecanismo de acción de estos fármacos se basa fundamentalmente en las modificaciones que pueden realizar en los canales de Na^+ y Ca^{++} (14,33).

En la actualidad existen muchos fármacos utilizados para el dolor neuropático desde que en 1942 se usara por primera vez la fenitoína para el tratamiento de la neuralgia del trigémino (29,34). Los más utilizados a día de hoy son la pregabalina y gabapentina, cuyas dosis máximas diarias van desde los 300-600 mg de la pregabalina hasta los 1200-3600 mg de la gabapentina (14,16,35).

Según el "*Neuropathic Pain Special Interest Group* (NeuPSIG)" de la "*International Association for the Study of Pain* (IASP)", basándose en "*Grading of Recommendations Assessment, Development, and Evaluation* (GRADE)", tanto los fármacos antiepilépticos como antidepresivos estarían incluidos en la primera línea de recomendación de tratamiento para el dolor neuropático (30).

3. *Opioides*

Los opioides son los fármacos analgésicos de amplio espectro más efectivos que existen para dolor de intensidad media o moderada, sin embargo, en procesos

crónicos su uso puede llegar a ser limitado. El mecanismo de acción de estos fármacos se basa en su acción a nivel de los receptores opioides. A día de hoy, la utilidad de los opioides en términos de seguridad y efectividad para el dolor neuropático no está definida. La limitación del uso de estos fármacos radica en la tolerancia y efectos secundarios que pueden provocar en el paciente, por lo que la vigilancia de estos signos y síntomas que puedan aparecer es realmente importante (36).

Los opioides más utilizados para el tratamiento del dolor neuropático son tramadol y oxicodona (14,37–40). Según neuPSIG, los opioides estarían incluidos en la segunda línea de tratamiento para el dolor neuropático (30).

4.   *Tratamientos tópicos*

Con respecto a los tratamientos tópicos para el dolor neuropático nos encontraríamos principalmente con dos fármacos de uso más común: parches de lidocaína 5% y parche de capsaicina 8%.

- Los parches de lidocaína 5% consisten en unos apósitos medicamentosos indicados fundamentalmente para el dolor neuropático tras infección por el virus del Herpes Zoster (neuralgia postherpética). Este apósito debe estar colocado a lo largo del área dolorosa durante 12 horas en un periodo de 24 horas. La gran ventaja de esta terapia es la seguridad y tolerabilidad, con el único efecto adverso posible en forma de reacciones cutáneas provocadas por la hipersensibilidad (41).

- El parche de capsaicina 8% es un tratamiento indicado en pacientes adultos con dolor neuropático periférico, sólo o en combinación con otros medicamentos para el dolor. La capsaicina es una sustancia química perteneciente al grupo de los anestésicos locales, cuyo origen se encuentra en una variante de las guindillas (42). Esta sustancia actúa como agonista de los TRPV1 (transient receptor potential vanilloid 1), activando los nociceptores cutáneos que expresan dicha sustancia, lo que provoca la

presencia de dolor y eritema. Tras la exposición a esta sustancia, dichos nociceptores pierden parte de su sensibilidad, lo que conlleva la aparición de alivio de dolor en el paciente. Esta perdida de sensibilidad es transitoria y temporal (43). En el caso de la capsaicina, no solo existe la presentación en parche al 8%, también se pueden encontrar dos versiones de este producto en cremas al 0,025% y 0,075% (44).

Además de los fármacos descritos, también existen otros fármacos menos habituales, pero que su uso en algunos casos está en expansión para el tratamiento del dolor neuropático como son la clonidina tópica, Toxina Botulínica A y perfusiones intravenosas de lidocaína, entre otros (30,45–47).

Con respecto a los tratamientos tópicos, en la mayoría de guías de recomendación se encuentran en un segundo nivel o escalón para el tratamiento del dolor neuropático, es decir, su utilización estaría indicada ante la ineficacia de fármacos orales o la imposibilidad del uso de los mismos (13,16,30,35,48).

Tratamientos no farmacológicos

Los tratamientos no farmacológicos se basan mayoritariamente en terapias intervencionistas con aplicación de energía, las cuales asumen el protagonismo del tratamiento del dolor neuropático periférico cuando los tratamientos farmacológicos no son suficientes para el alivio de dicho dolor.

1. *Estimulación nerviosa*

   a. Estimulación medular

La estimulación medular consiste en una cirugía mediante la que se implantan uno o más electrodos en el canal medular del paciente. Estos electrodos, conectados a un generador de corriente implantado, y mediante la programación de los parámetros asociados al tipo de estimulación como son frecuencia, ancho de pulso e intensidad, pretenden generar en el paciente una sensación agradable de

parestesia a lo largo de su área dolorosa que "enmascare" dicho dolor. A día de hoy comienzan a proliferar dispositivos que no generan dicha sensación de parestesia, sino que usan modos de estimulación de alta frecuencia o Burst®, denominados comúnmente como estimulaciones de tipo "*Free Paresthesia*" (49).

Su mecanismo de acción se basó, a priori, en la teoría de la puerta de entrada de Wall y Melzack, sin embargo a día de hoy todavía no se conoce fielmente el origen del alivio del dolor mediante estímulos eléctricos medulares (50).

Son múltiples los estudios que avalan su uso en dolor neuropático periférico, especialmente en casos de neuropatía diabética o neuralgia postherpética, entre otros (51,52).
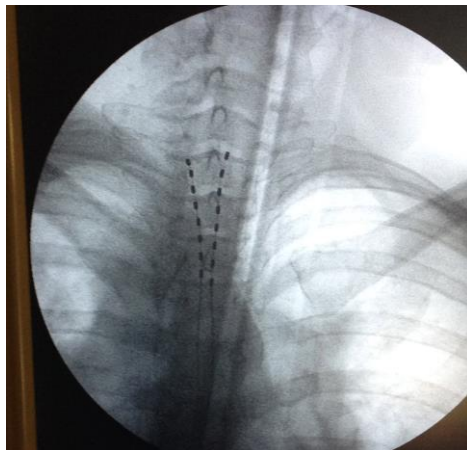

Imagen 1: Electrodos implantados en columna dorsal (Imagen propia)

Imagen 2: Modelo de sistema de neuroestimulación (Imagen propia)

b.   Estimulación nerviosa transcutánea (TENS)

La terapia TENS es otra alternativa para el tratamiento del dolor neuropático periférico, que consiste en la colocación de electrodos adhesivos en la piel conectados a un generador de corriente. Dicho generador puede ser modificado en términos de intensidad, duración y frecuencia, pudiendo programarse ésta última como baja frecuencia (igual o < 10 Hz) o alta frecuencia (50-100 Hz o superior) (53).

Su uso constituye un elemento más para el alivio del dolor, pudiendo ser combinado con tratamientos farmacológicos, sin embargo, la calidad de la evidencia de los estudios clínicos sobre esta terapia aún es relativamente baja (53).

c.   Estimulación nerviosa periférica (PNS)

Este tipo de terapia actúa de forma similar a la estimulación medular. La diferencia radica en la colocación del electrodo, ya que éste debe ser colocado en la región próxima al nervio periférico afectado. Su mecanismo de acción y los parámetros de ajuste son similares a la estimulación medular (54).

Su eficacia ha sido demostrada para patologías tales como cefalea en racimos, neuralgia postherpética, neuralgia del trigémino, neuralgia femorocutánea, entre otros (55,56).

2.   Radiofrecuencia

a.   Radiofrecuencia convencional

La radiofrecuencia es considerada como un procedimiento mínimamente invasivo para el tratamiento del dolor cuya técnica consiste en la introducción de una aguja a través de la piel que se coloca cercana a la localización de la zona afectada. Esta aguja va conectada a un generador de radiofrecuencia mediante el cual se aplica un

voltaje determinado que conlleva el aumento de temperatura en la zona de aplicación de la aguja. La finalidad de esta terapia es la destrucción tisular, y es conocida como radiofrecuencia convencional (57).

Una de sus grandes indicaciones es la neurolisis del ganglio de Gasser para la neuralgia del trigémino (58).

b. Radiofrecuencia pulsada

La radiofrecuencia pulsada es prácticamente similar a la convencional, sin embargo, su gran diferencia es que no tiene carácter destructivo en los tejidos. El generador de corriente realiza una actividad mediante pulsos cíclicos, por lo que la temperatura alrededor de la punta de la aguja no aumenta por encima de un nivel que pueda lesionar (42º). No existe un criterio único para definir la influencia de la radiofrecuencia pulsada en las estructuras nerviosas. Aunque su uso comienza a ser habitual para el manejo del dolor neuropático siendo una alternativa eficaz en la neuralgia postherpética, no queda del todo claro los beneficios reales en otros tipos de patología por dolor neuropático (58,59).

Centrándonos en el tratamiento no farmacológico de la neuropatía diabética, existen más terapias utilizadas en la literatura científica como son la terapia magnética (60–63), acupuntura (64–66), u otras terapias de estimulación nerviosa como PENS (Percutaneous electrical nerve stimulation) (67) o FREMS (Frequency-modulated electromagnetic neural stimulation) (68). Todas estas terapias tienen escasos ensayos clínicos aleatorizados publicados, y las principales revisiones y guías de recomendación de tratamiento para la NDD les otorgan un nivel bajo de recomendación o incluso ni las mencionan (13,14,16,30,35,48,69).

Escalas y cuestionarios de medición del dolor

A la hora de hablar del dolor es inevitable hablar también sobre su valoración, y dicha valoración la hacemos mediante el uso de cuestionarios o escalas. A lo largo de la literatura científica existen multitud de estudios sobre el dolor que obtienen

sus resultados a través del uso de escalas, sin embargo no existe un criterio único a la hora de la elección de una determinada escala o cuestionario, y también hay que tener en cuenta su nivel de validez.

De las escalas y cuestionarios más utilizados y revisados en estudios de diferentes ámbitos podemos destacar los siguientes:

1. Escalas numéricas

Es uno de los métodos mas comunes a la hora de realizar una valoración del dolor. Para el paciente se trata de un elemento de valoración bastante sencillo en el cual debe determinar en una escala de 0 a 10 o de 0 a 100 el nivel mínimo y máximo de dolor que percibe (70).

2. Escala análoga visual (EVA)

Al igual que con la escala numérica, se trata de un método de valoración sencillo de usar y de entender por parte del paciente. La escala EVA se basa en una línea dibujada en la que aparece en un extremo el 0 y en el otro extremo aparece el 10, siendo 0 la inexistencia de dolor y 10 el peor dolor imaginable (Figura 2). El paciente tiene que señalar su nivel de dolor a lo largo de esa línea (70).

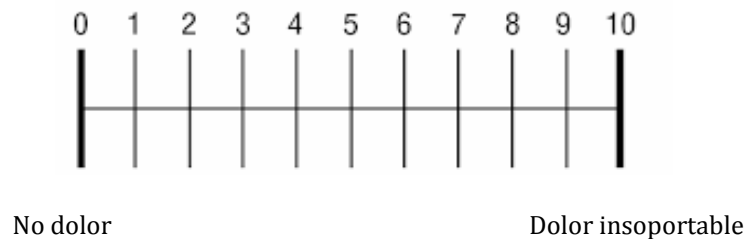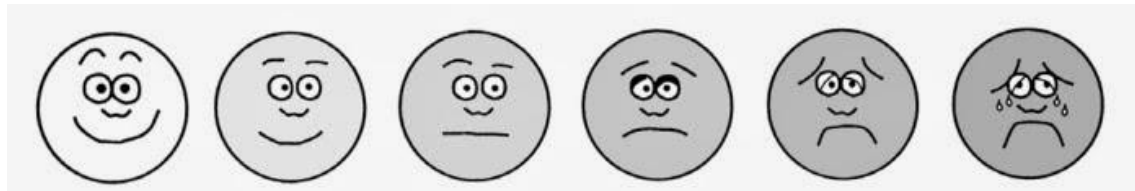No dolor   Dolor insoportable

Figura 2: Escala EVA

3.   Escala de imágenes faciales

Esta escala es de gran utilidad en pacientes pediátricos o personas con déficit intelectual (Figura 3). Se trata de una escala donde aparecen 6 caras que expresan de forma progresiva desde una cara llorosa a una cara de felicidad (71,72).

Sin dolor   Muchísimo Dolor

Figura 3: Escala de imágenes faciales (73)

4.   McGill Pain Questionaire (MPQ)

Uno de los más famosos y utilizados sistemas de evaluación multidimensional del dolor, creado en 1975 por el Dr. Ronald Melzack. Este instrumento de medida se basa en 4 subclases que son sensorial, afectiva, evaluativa y miscelánea del dolor, además de respuestas al Pain Rating Index (PRI), que contiene 78 descriptores del dolor y 20 subclases a su vez, y una escala de intensidad del dolor de 5 puntos (Present Pain Intensity (PPI)). Cuanto más alta sea la puntuación obtenida en MPQ, más alto será el nivel de dolor del paciente (74). También existe una versión corta de esta escala denominada SF-MPQ (75) (Figura 4).

Temporal I:
- A golpes
- Continuo

Temporal II:
- Periódico
- Repetitivo
- Insistente
- Interminable

Localización I:
- Impreciso
- Bién delimitado
- Extenso

Localización II:
- Repartido
- Propagado

Punción:
- Como un pinchazo
- Como agujas
- Como un clavo
- Punzante
- Perforante

Incisión:
- Como si cortase
- Como una cuchilla

Constricción:
- Como un pellizco
- Como si apretara
- Como agarrotado
- Opresivo
- Como si exprimiera

Tracción:
- Tirantez
- Como un tirón
- Como si estirara
- Como si arrancara
- Como si desgarrara

Térmico I:
- Calor
- Como si quemara
- Abrasador
- Como hierro candente

Térmico II:
- Frialdad
- Helado

Sensibilidad Táctil:
- Como si rozara
- Como un hormigueo
- Como si arañara
- Como si raspara
- Como un escozor
- Como un picor

Consistencia:
- Pesadez

Miscelánea Sensorial I:
- Como hinchado
- Como un peso
- Como un flato
- Como espasmos

Miscelánea Sensorial II:
- Como latidos
- Concentrado
- Como si pasara corriente
- Calambrazos

Miscelánea Sensorial III:
- Seco
- Como martillazos
- Agudo
- Como si fuera a explotar

Tensión Emocional:
- Fastidioso
- Preocupante
- Angustiante
- Exasperante
- Que amarga lavida

Signos Vegetativos:
- Nauseante

Miedo:
- Que asusta
- Temible
- Aterrador

Categoría Valorativa:
- Débil
- Soportable
- Intenso
- Terriblemente molesto

Indique la expresión que mejor refleja la intensidad del dolor, en su conjunto, en el momento actual
- Leve, débil, ligero
- Moderado, molesto, incómodo
- Fuerte
- Extenuante, exasperante
- Insoportable

Marque con una cruz sobre la línea, indicando cuanto dolor tiene actualmente

SIN DOLOR |___|___|___|___| **DOLOR INSOPORTABLE**

PRI-S [ ]   PRI-E [ ]   PRI-V [ ]   PRI-M [ ]   PRI-TOTAL [ ]

Número Palabras: [ ]   PPI: [ ]   EVA (0-10): [ ]

Figura 4: SF McGill Pain Questionnaire (75)

5.   Brief Pain Inventory (BPI)

Esta escala es uno de los instrumentos de medida multidimensional del dolor más usados hoy en día, proporcionando una percepción rápida de la intensidad del dolor así como interfiere este dolor en la funcionalidad del paciente. Originariamente se utilizaba solo en pacientes que presentaban un dolor de tipo

oncológico, sin embargo, su uso con el paso de los años ha sido validado para dolores crónicos no malignos entre otras patologías (76). Este instrumento permite a los pacientes valorar la intensidad del dolor en función de si es peor, si es menor, dolor de media e intensidad actual, además de siete dominios de funcionamiento como son la actividad general, estado de ánimo, la capacidad para caminar, el trabajo habitual, las relaciones con otras personas, el sueño, y el disfrute de la vida, todo ello reflejado en una escala de 0 a 10 (77,78).

De esta escala también cabe destacar la existencia de una versión más acotada denominada SF-BPI, la cual se usa con más frecuencia en investigaciones y aspectos clínicos, y estando validada en pacientes españoles con dolor de etiología no oncológica (79).

Además de estos 5 cuestionarios o escalas descritas anteriormente, también se encuentran descritas otras que tienen como finalidad la valoración del dolor de tipo neuropático. Entre las mas destacadas se encuentran las siguientes:

1. Neuropathic Pain Questionnaire (NPQ)

Esta herramienta creada por Krause y Backonja en 2003 consiste en un cuestionario de 12 ítems, donde los diez primeros están relacionados con la percepción del dolor y los otros dos con las situaciones que causan un cambio en dicho dolor. Estos 12 ítems se valoran en escalas de 0 a 100, y las puntuaciones obtenidas son multiplicadas por unos coeficientes predeterminados.

Tras el cálculo de la operación se predice que valores inferiores a 0 tendrán un dolor no neuropático, y valores iguales o superiores a 0 tendrán un dolor neuropático (80).

2. ID-PAIN

Se trata de un cuestionario breve autoadministrable creado por Portenoy en 2006 (81). Se componen de 3 apartados:

- Apartado 1: consta de dos preguntas relacionadas con la presencia de dolor, y si este está presente en cabeza o en forma de migraña.
- Apartado 2: muestra una imagen corporal donde el paciente debe señalar la localización del dolor.
- Apartado 3: consta de 6 preguntas relacionadas con las características del dolor en la última semana.

Para evaluar los resultados se valora solo el apartado 3, donde una respuesta afirmativa en las 5 primeras preguntas otorga 1 punto por cada una y negativa 0 puntos, y una respuesta positiva en la 6 pregunta otorga -1 punto. Puntuaciones totales entre -1 y 5 sugieren la presencia de componente neuropático (Anexo 1).

Este tipo de cuestionario tiene una adaptación y validación al castellano por parte de Rafael Gálvez y colaboradores en 2008 (82).

3. <u>Douleur Neuropathique en 4 questions (DN4)</u>

El cuestionario DN4 fue creado por Bouhassira y colaboradores en 2005 (83). Está compuesto por un total de 10 ítems divididos en 4 secciones, donde los 7 primeros corresponden a preguntas relacionadas con las características del dolor y los 3 restantes con un examen neurológico de la zona dolorosa. Las respuestas afirmativas son puntuadas con 1 punto y las negativas con 0 puntos, por lo que la máxima puntuación es 10 y la mínima es 0. Para considerar la presencia de dolor neuropático se debe obtener una puntuación igual o superior a 4 puntos (Anexo 2).

Al igual que en el cuestionario ID-Pain, existe una versión española validada realizada por Concepción Pérez y colaboradores en 2007 (84).

4. <u>Leeds assessment of neuropathic symptoms and signs (LANSS)</u>

La escala LANSS fue la primera herramienta desarrollada para la valoración del dolor neuropático, en concreto fue creada por Bennett en 2001 (85). Esta escala,

realizada por un entrevistador entrenado para ello, consta de ítems agrupados en dos secciones (Anexo 3).

En la primera sección se realizan cinco preguntas relacionadas con las características propias del dolor neuropático, otorgándose 0 puntos en caso de ausencia de manifestación, y de 1 a 5 puntos según cada ítem si existe dicha sintomatología.

En la segunda sección se realiza un análisis sensorial mediante dos preguntas para las cuales se utilizan instrumentos como una torunda de algodón y una aguja. En caso de no obtenerse respuesta a la estimulación mediante estos instrumentos se obtendrá una puntuación de 0, y en caso positivo se obtendrán 5 y 3 puntos respectivamente.

Una puntuación total igual o superior a 12 indica la presencia de mecanismos neuropáticos que contribuyen al dolor del paciente.

Para esta escala también existe una versión validada al español a cargo de Concepción Pérez y colaboradores en 2006 (86).

5. painDETECT

PainDETECT es un cuestionario auto-administrado desarrollado para detectar de forma rápida la presencia de un componente neuropático del dolor. Este cuestionario fue por primera vez desarrollado y validado en alemán por Freynhagen y colaboradores en 2005 (87). Esta escala consta de 4 bloques diferenciados (Anexo 4):

- Bloque 1: contiene 3 ítems relacionados con la intensidad de dolor actual y en las últimas 4 semanas. Se valora la intensidad mediante una escala Likert de 11 puntos donde 0 es "no dolor" y 10 es "máximo dolor".
- Bloque 2: se representan 4 gráficas que describen el curso del dolor. Las puntuaciones van desde -1 a + 1 según el ítem seleccionado.

- Bloque 3: el tercer bloque representa un mapa sensorial caracterizado por una figura humana en posición frontal y de espaldas. En ella se le pide al paciente que dibuje donde localiza el dolor, si existen la presencia de irradiación, y en ese caso que dibuje también hacia donde se le irradia. En el caso que la respuesta acerca de la irradiación sea positiva se sumaran dos puntos.

- Bloque 4: consta de 7 ítems relacionados con las características del dolor y sus factores asociados. Se valora mediante escala Likert de 6 puntos donde 0 es "nunca" y 5 es "muy intenso"

La puntuación total de esta escala oscila entre el 0 y los 35 puntos, interpretándose el resultado de la siguiente manera:

- Puntuación de 0 a 12: poca probabilidad de componente neuropático (<15%).
- Puntuación de 12 a 18: resultado ambiguo, aunque puede existir componente neuropático.
- Puntuación de 18 a 35: alta probabilidad de presencia de componente neuropático (>90%).

Al igual que en escalas anteriores, existe una versión validada al español por José de Andrés y colaboradores en 2012 (88).

Además de las escalas existentes y analizadas anteriormente, existe también una herramienta para la detección del dolor neuropático localizado llamada "Screening Tool", facilitada por la Sociedad Española del Dolor (89).

Esta herramienta permite confirmar la existencia del dolor neuropático localizado mediante 4 ítems relacionados con el principal motivo de consulta y apartados relacionados con la anamnesis, anatomía, pruebas sensoriales y extensión de la zona dolorosa. A través de las respuestas de los diferentes apartados se comprueba mediante un algoritmo la presencia de dolor neuropático localizado.

Antecedentes y estado actual de conocimiento sobre el problema de investigación

La neuropatía diabética dolorosa es una enfermedad que viene siendo investigada desde hace varias décadas, siendo una línea común el desconocimiento de la etiología y la presencia de los mismos signos y síntomas.

A principios de los años 70 se comenzaron a describir las características del dolor asociado a la neuropatía diabética. Lo describían como una sensación de quemazón, parestesias y dolores punzantes, que tenían predominio nocturno, y podían provocar la presencia de insomnio y depresiones. Su distribución por sexos se creía predominantemente masculina, y el inicio de la terapia con insulina a veces mejoraba los síntomas y otras los empeoraba inexplicablemente. El tratamiento era complejo, con una prolongación de los síntomas importante, siendo el uso de antidepresivos y analgésicos no adictivos las preferencias farmacológicas para su cura. Se entendía que los síntomas que padecían los pacientes por esta enfermedad podían durar desde pocos meses hasta dos años (90–93).

Desde finales de los años 70 a finales de los 80, la literatura científica existente refleja el uso de diversos tratamientos para la NDD diferentes a los utilizados tradicionalmente, de todos ellos caben destacar los siguientes.

- Infusión subcutánea de insulina: los estudios que analizan dicha terapia corren a cargo de Boulton y colaboradores en 1982 (94) y Bertelsmann y colaboradores en 1987 (95). En el primero se realiza un análisis de la efectividad de la aplicación de esta terapia en 9 pacientes a los que se le realiza una medición del dolor a las 6 semanas y a los 4 meses; se concluye que, además del beneficio obtenido en cuanto a cifras de glucemia, el dolor en estos pacientes disminuye significativamente, sin embargo, no excluyen el efecto placebo y refieren la dificultad real de medición de los síntomas del dolor en este tipo de pacientes. En el segundo estudio se analiza la terapia en 15 pacientes a lo largo de 12 meses, en los cuales

reportan, al igual que en el estudio de Boulton y colaboradores, una mejoría en las cifras de glucemia y en la percepción del dolor, además de una mejoría en la función de los nervios periféricos.

- Inhibidor de la aldosa reductasa: este fármaco también llamado Sorbinil fué analizado en tres ensayos clínicos con grupo placebo, dos de ellos a cargo de Jaspan y colaboradores (96), en los que se medía la percepción del dolor y la función nerviosa. En todos ellos se obtiene en la mayoría de los pacientes una disminución del dolor (incrementándose éste cuando detenían la toma de medicación) y una mejoría en la función nerviosa autónoma (96–98). Sin embargo, en un ensayo clínico a cargo de Lewin y colaboradores (99), se estudió la administración de Sorbinil 200 mg diarios en 4 semanas a 13 pacientes en los que se analizó la función nerviosa sensitiva, motora y autónoma, la duración del sueño y el nivel del dolor; en ninguno de estos aspectos se reportó mejoría, no encontrándose beneficio ninguno con el tratamiento mediante Sorbinil.

- Perfusión intravenosa de lidocaína: se describen varios artículos en la literatura científica con el uso de infusiones de lidocaína a 5 mg/kg de peso corporal. Todos estos artículos han sido llevados a cabo por Kastrup y colaboradores donde se analizan los signos y síntomas de neuropatía además del nivel del dolor, determinándose como una terapia efectiva en la reducción del dolor (100–102).

A finales de los años 80 y principios de los 90 nos encontramos que en la literatura científica comienzan a surgir estudios que analizan la efectividad de la terapia mediante capsaicina en la NDD. La capsaicina es una sustancia que proviene de los pimientos picantes o guindillas, cuyo mecanismo de acción en humanos se basa en la deplección de la sustancia P, principal neurotransmisor del dolor, a través de las fibras nerviosas aferentes nociceptivas tipo C (42). El auge del tratamiento de capsaicina se basó en un estudio realizado por Ross y Varipapa en 1989 donde reportaron dos casos de pacientes diabéticos con dolor neuropático que fueron tratados satisfactoriamente con capsaicina tópica (103). A raíz de ahí comenzaron

a surgir multitud de estudios en los que analizaban su efectividad como terapia tópica al 0.075% y dando resultados realmente positivos en cuanto a alivio del dolor, por lo que rápidamente comenzaron a recomendar e incluir su uso como tratamiento habitual en la NDD (103–106). Es tal la revolución del tratamiento de la NDD con capsaicina que se crea un grupo de estudio denominado "The Capsaicin Study Group" formado por profesionales de prestigio en este ámbito, los cuales aportan dos estudios destacados en los que mediante ensayos clínicos aleatorizados con grupo control analizan el alivio del dolor, la presencia de efectos adversos y la influencia del beneficio de la terapia en las actividades de la vida diaria. Los resultados que obtienen señalan a la capsaicina tópica al 0.075% como un tratamiento, sólo o en combinación con otras terapias, efectivo para la NDD (107,108).

En la década de los 90 se siguen desarrollando investigaciones en el tratamiento de la NDD. Además de la continua investigación con capsaicina, se realizaron estudios destacables como la aplicación de clonidina tópica mediante parches cuyos resultados no son muy positivos en términos de alivio del dolor, y sugieren la necesidad de realizar mas ensayos clínicos sobre esta terapia para poder determinar qué tipo de paciente en concreto puede beneficiarse de ella (109,110). La mexiletina, fármaco oral derivado de la lidocaína, es otro de los tratamientos analizados en esta época. Existen varios artículos donde se estudia su uso a dosis diarias de 10 mg/kg de peso, 225 mg, 550 mg y 675 mg, siendo ésta última la más efectiva en cuanto a alivio del dolor se refiere. Dichos artículos destacan también la seguridad del fármaco, la escasez de efectos secundarios, y sobre todo la ausencia de problemas cardiovasculares asociados (111–114).

Surge también durante esta década los primeros estudios que analizan las terapias eléctricas y la acupuntura en los pacientes con NDD. En un primer artículo publicado en 1997 por Armstrong y colaboradores se evidenció por primera vez la inexistencia de estudios que valorasen la terapia física en pacientes con NDD (115). En este estudio piloto se aplicó, mediante electrodos, a 10 pacientes una corriente pulsada a 100 Hz, con una intensidad de 50 V durante 10 minutos por cada hora de terapia (8 horas por la noche en total). El seguimiento de estos

pacientes se realizó durante 4 semanas más 1 mes posterior sin terapia, obteniéndose una reducción significativa del dolor mediante escala VAS y sugiriendo la necesidad de realizar más ensayos clínicos que certifiquen los resultados de este estudio piloto. En un segundo artículo publicado en 1999 por Somers se reporta un caso clínico de una paciente de 73 años con NDD severa a la que se le aplica la terapia mediante TENS en zona lumbar (116). A dicha paciente se la aplica la terapia TENS en fase inicial a 80 Hz durante 20 minutos al día, terminando la paciente por auto-administrarse la terapia durante 1-2 horas al día con predominio nocturno. Los resultados obtenidos sugieren la efectividad de la terapia y la necesidad de más estudios relacionados con ella para aliviar la NDD. Un tercer estudio analiza el uso de la acupuntura para el alivio de la NDD en 46 pacientes aplicándola mediante los puntos acupunturales descritos en la Medicina Tradicional China durante 6 sesiones (1 mes aproximadamente) (117). Tras el análisis de los resultados se concluye, al igual que en los casos anteriores, la necesidad de más estudios de características similares y la presencia de la acupuntura como una alternativa terapéutica a las terapias farmacológicas convencionales de tratamiento de la NDD.

Otro acontecimiento importante a finales de la década de los 90 es la aparición de los primeros estudios que valoran el tratamiento de la NDD con opioides o con gabapentina. En el primer caso, los dos estudios más relevantes corren a cargo de Harati y colaboradores, y en ellos se valora el tratamiento con tramadol a corto plazo (42 días) y largo plazo (6 meses) a dosis diarias (como máximo) de 400 mg con resultados positivos en cuanto a alivio de dolor, pero la aparición de algunos efectos no deseados como somnolencia o nauseas, aunque según los autores, mejor tolerados por los pacientes que los efectos secundarios de antidepresivos y antiepilépticos (38,118). En el segundo caso comienzan a aparecer estudios que analizan la efectividad de la gabapentina en el tratamiento de la NDD, en concreto en el artículo publicado por Gorson y colaboradores se administra gabapentina a 19 pacientes (21 pacientes placebo) a dosis máxima de 900 mg/día siendo mínimamente efectivo en los mismos y reclamando la posibilidad de mayor efectividad en estudios que aumenten la dosis diaria (119). Otros artículos publicados al respecto analizan lo reclamado en el artículo de Gorson, la

administración de gabapentina a dosis superiores (3600 mg/día máximo) obteniéndose alivio importante del dolor en los pacientes con NDD (120).

A partir del año 2000 la literatura científica en torno al tratamiento de la NDD comienza a ser muy amplia y diversa. Empiezan a proliferar estudios en los que analizan todos los tratamientos farmacológicos y/o no farmacológicos para la NDD con la finalidad de crear líneas de recomendación al respecto (121–124). También comienzan a surgir estudios que analizan la combinación de fármacos para el tratamiento de la NDD, como por ejemplo gabapentina y venlafaxina (125), paroxetina o citalopran más gabapentina (126) o amitriptilina y duloxetina (127). Además de todo ello, siguen surgiendo nuevos estudios sobre terapias no usadas anteriormente en la NDD como son por ejemplo la pregabalina (128–130), zonisamida (131), parches de lidocaína al 5% (132,133) o compuestos de nitrato en forma de parches o sprays (134,135).

Toda esta aparición masiva a lo largo de los años de contenido científico en torno al tratamiento de la NDD desemboca en la creación de diversas guías de recomendación o revisiones de la literatura por parte de asociaciones o grupos especializados en la materia. A día de hoy, se pueden considerar como las más relevantes las siguientes:

- Revisiones Cochrane: se han descrito numerosas revisiones sobre el tratamiento del dolor neuropático elaboradas y publicadas bajo las recomendaciones de este reconocido organismo como es Cochrane. En ellas se han revisado tratamientos enfocados no solo para el dolor neuropático en general, sino también para la NDD. Entre las revisiones más destacadas nos encontramos las siguientes:
  - Opioides para el dolor neuropático (36).
  - Antidepresivos para el dolor neuropático (136).
  - Duloxetina para el tratamiento de la neuropatía dolorosa, el dolor crónico o la fibromialgia (137).
  - Inhibidores de la aldosarreductasa para el tratamiento de la polineuropatía diabética (138).

o Capsaicina tópica (baja concentración) para el dolor neuropático crónico en adultos (44).

o Farmacoterapia combinada para el dolor neuropático en adultos (139).

• Revisión sistemática de NeuPSIG: como ya se mencionó anteriormente, se trata de una revisión sistemática con meta-análisis realizada acorde a GRADE (*Grading of Recommendations, Assessment, Development and Evaluation*) sobre farmacoterapia para el tratamiento del dolor neuropático en adultos. Fueron incluidos 229 artículos sobre terapias farmacológicas para la NDD, incluidas también las terapias farmacológicas combinadas. Los resultados obtenidos se reflejan tabla 3 (30):

Clasificación GRADE	Fármacos	Dosis diaria	Recomendaciones
FUERTE PARA	Gabapentina	1200 – 3600 mg TID	Primera línea
	Gabapentina ER/enacarbil	1200-3600 mg BID	Primera línea
	Pregabalina	300 – 600 mg BID	Primera línea
	IRSN duloxetina/venlafaxina	60 – 120 QD (duloxetina), 150 – 225 mg QD (venlafaxina ER)	Primera línea
	TCA	25 – 150 mg QD o BID	Primera línea
DÉBIL PARA	Parche capsaicina 8%	1-4 parches en el área dolorosa durante 30-60 minutos cada 3 meses	Segunda línea (PNP)
	Parche lidocaína 5%	1-3 parches en el área dolorosa hasta 12 horas	Segunda línea (PNP)
	Tramadol	200 – 400 mg BID (tramadol ER) o TID	Segunda línea
	Toxina botulínica A (SC)	50–200 unidades en el área dolorosa cada 3 meses	Tercera línea: uso especialista (PNP)
	Opioides fuertes	Dosificación individualizada	Tercera línea
INCONCLUSO	Terapia combinada		
	Crema capsaicina		
	Carbamacepina		
	Clonidina tópica		
	Lamotrigina		
	Lacosamida		
	Oxcarbacepina		
	Tapentadol		
	Topiramato		
	Zonisamida		
DÉBIL CONTRA	Cannabionides		
	Valproato		
FUERTE CONTRA	Levetiracetam		
	Mexiletina		

Tabla 3: Recomendaciones basadas en la clasificación GRADE (30)

- <u>Guía clínica NICE</u>: se trata de una guía clínica elaborada por *National Institute for Health and Care Excellence* (en adelante NICE) sobre tratamiento farmacológico del dolor neuropático para personal no especialista en dolor (140). Esta guía recoge 115 estudios sobre dolor neuropático, de los cuales 11 tienen un origen central, 16 un origen mixto y 88 un origen periférico. Las recomendaciones otorgadas para este último, donde se encuentra la NDD, serían las siguientes:

  o Como tratamiento inicial elegir entre los fármacos amitriptilina, duloxetina, gabapentina o pregabalina.

  o Si uno de los tratamientos iniciales elegidos no funciona o no es bien tolerado, utilizar otro de los mencionados anteriormente, cambiándolo a su vez si sigue sin funcionar el elegido.

  o Considerar el uso de tramadol sólo en los casos agudos donde sea necesaria analgesia de rescate.

  o Considerar la capsaicina tópica en forma de crema como tratamiento en dolor neuropático periférico localizado en pacientes que no deseen o no toleren fármacos orales.

- <u>Guía EFNS</u>: se trata de una guía elaborada por la *European Federation of Neurological Societies* que recoge un total de 64 ensayos clínicos aleatorizados controlados sobre fármacos vs placebo o comparaciones. En esta guía se incluye un apartado para polineuropatías dolorosas tanto en pacientes diabéticos como no diabéticos cuyas recomendaciones se pueden observar en la tabla 4 (13):

Etiología	Nivel A para eficacia	Nivel B para eficacia	Nivel C para eficacia	Nivel A/B para ineficacia o resultados discrepantes	Recomendaciones de primera línea	Recomendaciones de segunda y tercera línea
Neuropatía diabética dolorosa	Duloxetina Gabapentina-morfina TCA Agonistas de nicotina Derivados del nitrato Oxicodona Pregabalina Tramadol solo o tramadol + paracetamol Venlafaxina ER	Toxina botulínica Dextrometorfano Gabapentina/venlafaxina Levodopa	Carbamacepina Fenitoína	Crema de capsaicina Lacosamida Lamotrigina Memantine Mexiletina Antagonistas NK1 Oxcarbacepina IRSS Clonidina tópica Topiramato Valproato Zonisamida	Duloxetina Pregabalina Gabapentina TCA Venlafaxina ER	Opioides Tramadol

Tabla 4: Clasificación de la evidencia según el fármaco en dolor neuropático de origen diabético (13).

- <u>Revisión AAN</u>: se trata de una revisión sistemática sobre los tratamientos para la NDD realizada por la *American Academy of Neurology* (en adelante AAN)*, the American Association of Neuromuscular and Electrodiagnostic Medicine*, y *the American Academy of Physical Medicine and Rehabilitation* (48)*.* Se trata de la única revisión que incluye terapias no farmacológicas para el tratamiento de la NDD. En la tabla 5 se puede ver el nivel de recomendación de las diferentes terapias analizadas en la revisión:

	Fármaco recomendado y dosis	No recomendado
Nivel A	Pregabalina 300-600 mg/día	
Nivel B	Gabapentina 900-3600 mg/día	Oxcarbacepina
	Valproato sódico 500-1200 mg/día	Lamotrigina
	Venlafaxina 75-225 mg/día	Lacosamida
	Duloxetina 60-120 mg/día	Clonidina
	Amitriptilina 25-100 mg/día	Pentoxifilina
	Dextrometorfano 400 mg/día	Mexiletina
	Sulfato de morfina, dosificado hasta 120	Magnetoterapia

mg/día	Laserterapia a baja intensidad
Tramadol 210 mg/día	Reiki
Oxicodona 37 mg (media), 120 mg (máximo)	
Capsaicina 0,075% QID	
Spray de dinitrato de isosorbida	
Estimulación eléctrica, estimulación nerviosa percutánea, x 3-4 semanas	

Tabla 5: Resumen de recomendaciones según AAN (48)

- <u>Guía de práctica clínica AACE</u>: realizada por *American Association Of Clinical Endocrinologists* (en adelante AACE*) y American College Of Endocrinology*, esta guía de práctica clínica surge para desarrollar un plan de cuidados para la comprensión de la DM (69). En ella se hace referencia al manejo de la NDD en su pregunta número 11: ¿Cómo se diagnostica y se trata la neuropatía en los pacientes con DM?. A esta pregunta la AACE responde lo siguiente:

  o Antidepresivos tricíclicos, anticonvulsionantes e inhibidores de la recaptación de serotonina y noradrenalina deben ser considerados para el tratamiento de la NDD, con un grado de recomendación A y un nivel 2 de evidencia.

- <u>Recomendaciones ADA</u>: se trata de un documento creado por la American Diabetes Association (en adelante ADA) sobre aspectos como la prevención, diagnostico evaluación y tratamiento, entre otros, de neuropatías diabéticas, fundamentalmente polineuropatía simétrica distal y neuropatía cardiovascular autónoma (14). En concreto, en el apartado de tratamiento del dolor, la ADA realiza las siguientes recomendaciones:

  o Considerar la pregabalina o duloxetina como tratamiento inicial de los síntomas del dolor neuropático en DM. Grado de recomendación A.

o   Gabapentina también puede ser usado como tratamiento inicial, teniendo en cuenta el estatus socio-económico del paciente, comorbilidades y potenciales interacciones farmacológicas. Grado de recomendación B.

o   Aunque su uso no está aprobado por la *Food and Drug Administration* (en adelante FDA), los antidepresivos tricíclicos son efectivos en el dolor neuropático en DM pero deben ser usados con precaución por alto riesgo de efectos adversos serios. Grado de recomendación B.

o   Debido al alto riesgo de adicción y otras complicaciones, los opioides, incluidos tapentadol y tramadol, no se recomiendan como tratamientos de primera ni segunda línea para el dolor en pacientes con polineuropatía simétrica distal.

Además de todas las terapias vistas anteriormente cabe destacar otro tipo de terapia que, a pesar de no ser realizada ni manejada por los profesionales de la podología sino por facultativos anestesistas y/o neurocirujanos y personal de enfermería, constituye un cuerpo de conocimientos interesante para el podólogo ya que se trata de una terapia cuyo uso está aumentando notablemente en los últimos años. Esta terapia es la neuroestimulación, descrita en apartados anteriores, cuya evidencia como tratamiento de la NDD se inicia con el estudio de Tesfaye y colaboradores en 1996 donde se aplica en 10 pacientes no respondedores a tratamiento convencional para la NDD, donde 8 de los cuales refieren un alivio significativo del dolor tras el implante del neuroestimulador (141). A raíz de este estudio han sido diversos los artículos que analizan esta terapia en la NDD, sobre todo en los últimos años, y en algunos de ellos se evidencia el uso de diferentes tipos de estimulación que mejoren el alivio del dolor del paciente (52,142–147).

Una vez conocida la patología de estudio y los tratamientos existentes se procederá a revisar, mediante meta-análisis, la efectividad de algunos de los tratamientos mencionados anteriormente, con el fin de contribuir a la actualización y aumento de conocimientos sobre la NDD que puedan servir de

ayuda a los profesionales sanitarios en la toma de decisiones para tratar a los pacientes afectados por esta enfermedad.

OBJETIVOS

El propósito del estudio fue analizar mediante meta-análisis las alternativas terapéuticas existentes para el tratamiento de la NDD, para lo cual se marcaron los siguientes objetivos:

Objetivo general

- Determinar cuáles son las terapias más efectivas para el tratamiento de la NDD.

Objetivos secundarios

- Determinar las líneas de tratamiento según los resultados obtenidos.
- Analizar las revisiones más importantes existentes para el tratamiento de la NDD.
- Comprobar si existe evidencia sobre tratamientos para la NDD mediante terapias combinadas.

MATERIAL Y MÉTODO

Pregunta de investigación (PICO)

La base de nuestro estudio es dar resolución a la pregunta de investigación: *¿cuál de los tratamientos farmacológicos orales, tópicos y físicos es el más efectivo para el alivio del dolor producido por la neuropatía diabética?.* Para ayudar en la elaboración de esta pregunta y conseguir enfocar más el objeto de estudio es de gran utilidad la herramienta PICO. El acrónimo PICO corresponde a los siguientes ítems:

- P: Participantes
- I: Intervenciones
- C: Comparaciones
- O: Outcome (resultados)

La adaptación de la pregunta PICO a la pregunta de investigación del estudio muestra las siguientes características que se observan en la tabla 6:

P	Participantes	Personas con neuropatía diabética dolorosa
I	Intervenciones	Tratamiento del dolor mediante terapias farmacológicas orales, tópicas o físicas únicas
C	Comparaciones	Grupo control (placebo)
O	Resultados	Nivel de dolor

Tabla 6: Pregunta PICO del estudio

Diseño de investigación

Se trata de un estudio tipo revisión sistemática con meta-análisis. El meta-análisis consiste en el análisis estadístico del conjunto de resultados obtenidos en diferentes ensayos clínicos sobre una misma cuestión, con la finalidad de

evaluarlos de manera conjunta (148). Este meta-análisis ha sido realizado con forme a las normas incluidas en la declaración PRISMA (149).

Este estudio fue llevado a cabo en el Departamento de Podología, dentro de la Facultad de Enfermería, Fisioterapia y Podología de la Universidad de Sevilla, en el periodo comprendido entre Octubre 2014 a Noviembre 2017.

Criterios de inclusión y exclusión

Para la selección de los estudios clínicos del meta-análisis, en primer lugar se siguieron una serie de *criterios de inclusión y exclusión* a fin de garantizar una correcta homogeneidad en la obtención de datos de dichos estudios. Estos criterios se desglosan a continuación siguiendo una estructura similar a la herramienta PICO anteriormente descrita:

1. *Criterios de inclusión:*
    a) *Tipos de estudio*
       - Se incluyeron en la búsqueda ensayos clínicos aleatorizados (en adelante ECA).

    b) *Tipos de participantes*
       - Se incluyeron estudios en los que los participantes presentaran como patología principal neuropatía diabética dolorosa (denominado también como dolor neuropático en paciente con DM).
       - Los pacientes a incluir son mayores de edad, indiferentemente del sexo, con indiferencia del tiempo de evolución del dolor neuropático.

    c) *Tipos de intervención*
       - Todos aquellos estudios en los que el tratamiento para la neuropatía diabética dolorosa fuera de tipo farmacológico oral, tópica o terapia física frente a grupo control.

d) Tipos de comparaciones

• Se incluyeron exclusivamente estudios que tuvieran como comparación un grupo control (placebo).

e) Tipos de resultados

• Se incluyeron los estudios cuyos resultados midieran el nivel de dolor mediante escalas validadas.

2. *Criterios de exclusión*

   a) Tipos de estudio

   • Se excluyeron todos los estudios cuya calidad metodológica no fuera adecuada tras la valoración mediante escala JADAD.

   • Se excluyeron los estudios que no proporcionaban los suficientes datos estadísticos que posibilitaran la realización del meta-análisis.

   b) Tipos de participantes

   • Los participantes menores de edad, sin historia de diabetes ni dolor neuropático provocado por dicha patología, fueron excluidos del meta-análisis.

   c) Tipos de intervención

   • Los estudios cuya intervención consistió en la aplicación de terapias cuyo uso no está acreditado o evidenciado como válido para la patología que describimos en al menos uno de los organismos oficiales principales (véase *Food and Drug Administration (FDA), European Medicine Agency (EMA), Agencia Española del Medicamento y Productos Sanitarios (AEMPS)*), o en alguna de las revisiones más destacadas realizadas por sociedades científicas, y aquellos que utilizaban terapias combinadas fueron excluidos.

d) _Tipos de comparaciones_

- Aquellos estudios cuya metodología incluyó un grupo control mediante otro tipo de terapia, o sin grupo control, fueron excluidos.

e) _Tipos de resultados_

- Se excluyeron los estudios cuyos resultados no expresaban la valoración del dolor tras la terapia aplicada o los datos obtenidos no eran válidos para el análisis estadístico mediante meta-análisis, además de aquellos cuya herramienta para la valoración del dolor no se encontrase validada.

Fuentes de información utilizadas

Para la obtención de los estudios que componen el meta-análisis se procedió al uso de bases de datos digitales cuyo contenido estuviera relacionado con las Ciencias de la Salud. Para acceder a ellas se utilizaron los enlaces digitales ubicados en la página web de la biblioteca de Ciencias de la Salud de la Universidad de Sevilla (www.bib.es.us/salud) y en la web de la Biblioteca Virtual del Sistema Sanitario Público Andaluz (BVSSPA). Las bases de datos consultadas fueron:

1. **Pubmed**: se trata de un motor de búsqueda de libre acceso a través del cual se accede a la base de datos _MEDLINE_, producida por la Biblioteca Nacional de Medicina de los Estados Unidos, y caracterizada por ser una de las bases de datos científicas mas importantes.

2. **Web of Science (WOS)**: servicio en línea generado por la empresa *Thomson Reuters* e integrado en *ISI Web of Knowledge*, que proporciona acceso a recursos científicos relacionados con las Ciencias de la Salud. En la búsqueda mediante WOS se integraron por defecto otras bases de datos tales como CCC (Current Contents Connect), DIIDW (Derwent Innovation Index), KJD (Korean Journal Database), MEDLINE, RSCI (Russian Science Citation Index) y SCIELO.

Protocolo de búsqueda

a) Paso nº1:

Se realizó una búsqueda en las bases de datos analizadas en el apartado anterior. Para ello se usaron la combinación de los términos "pain", "painful diabetic neuropathy", "diabetic neuropathy", "peripheral diabetic neuropathic pain", "neuropathic pain", "treatment", "therapy", mediante los operadores boleanos AND/OR, y el uso de truncamientos en los casos que fuera necesario. Las estrategias de búsqueda para las bases de datos analizadas se muestran en la tabla 7.

PUBMED		WEB OF SCIENCE (WOS)
Recent queries in pubmed		
#13,"Search ((("painful peripheral neuropathy) AND diabet*)) AND ((treatment) OR therap*)"	#15	#10 AND #5 *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#12,"Search (("painful peripheral neuropathy) AND diabet*"	#14	#9 AND #5 *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#11,"Search ((((((neuropat*) AND pain) AND diabet*)) AND peripheral)) AND ((treatment) OR therap*)"	#13	#8 AND #5 *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#10,"Search ((((neuropat*) AND pain) AND diabet*)) AND peripheral"	#12	#7 AND #5 *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#9,"Search ((neuropat*) AND pain) AND diabet*"	#11	#6 AND #5 *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO*

		Idioma de búsqueda=Auto
#8,"Search ((((treatment) OR therap*)) AND ((""neuropathic pain"") AND diabet*)"	#10	**TEMA:** ("peripheral diabetic neuropathic pain") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#7,"Search (treatment) OR therap*"	#9	**TEMA:** ("peripheral diabetic neuropathy") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#6,"Search (""neuropathic pain"") AND diabet*"	#8	**TEMA:** ("peripheral diabetic neuropathy") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#5,"Search (""diabetic neuropathy"") AND (Treatment OR therapy)"	#7	**TEMA:** ("painful diabetic neuropathy") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#4,"Search ((""painful diabetic neuropathy"") AND treatment) AND therapy"	#6	**TEMA:** ("diabetic neuropathy") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#3,"Search ((""painful diabetic neuropathy"") AND treatment) OR therapy"	#5	**TEMA:** (treat* OR therap*) *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#2,"Search (""painful diabetic neuropathy"") AND Therapy"	#4	**TEMA:** ("diabetic neuropathy" AND (treat* OR therap*)) *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
#1,"Search ""painful diabetic	#3	**TEMA:** ("peripheral diabetic neuropathic

neuropathy"""		pain" AND (treat* OR therap*)) *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
	#2	**TEMA:** ("painful diabetic neuropathy" AND (treat* OR therap*)) *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*
	#1	**TEMA:** ("painful diabetic neuropathy") *Bases de datos= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO* *Idioma de búsqueda=Auto*

Tabla 7: Estrategia de búsqueda de las bases de datos analizadas

b) Paso nº 2:

Para obtener resultados más exactos a los criterios de inclusión y exclusión utilizados en este estudio se aplicaron filtros con el fin de centrar la búsqueda en ensayos clínicos aleatorizados, ya sea mediante la propia base de datos o a través del acceso a la biblioteca de Ciencias de la Salud de la Universidad de Sevilla y a la BVSSPA.

c) Paso nº3:

Se eliminaron los artículos duplicados tras la búsqueda en las diferentes bases de datos.

Selección de los estudios

Tras la realización de la búsqueda y obtención de los resultados se procedió al análisis de los mismos con el fin de incluirlos en el meta-análisis.

Para ello se procedió a ordenar los estudios seleccionados según el tipo de terapia utilizada, ya sea farmacológica oral, tópica o física. Una vez clasificados los estudios según terapia, se analizaron individualmente siguiendo la metodología de la pregunta de investigación PICO, para a su vez, determinar si se cumplían o no los criterios de inclusión y exclusión determinados previamente.

Con respecto a los resultados obtenidos, para evitar la exclusión de algunos estudios que se consideraron potencialmente seleccionables y que no se pudieron obtener a texto completo o faltaban datos estadísticos relevantes, se recurrió a dos estrategias consensuadas con el tutor y directores de tesis:

1. *Préstamo interbibliotecario*

En los casos que no fue posible el acceso al artículo mediante los recursos electrónicos mencionados en apartados anteriores, se procedió a su búsqueda y solicitud a través de la Biblioteca de la US, en concreto a través del servicio de préstamo interbibliotecario.

Tras el análisis de los artículos solicitados mediante el servicio de préstamo interbibliotecario, se decidió que no cumplían los requisitos necesarios para su inclusión en el meta-análisis.

2. *E-mail autores*

Aquellos artículos que fueron determinados potencialmente seleccionables para el meta-análisis, pero que no incluían ciertos datos que nos permitían poder realizar nuestro análisis estadístico, se obtuvieron las direcciones de correo electrónico de los autores para la posterior solicitud a los mismos de los datos ausentes e imprescindibles en nuestro estudio. Sin embargo, de todos los e-mail enviados, no se obtuvo ninguna respuesta por parte de dichos autores. (Anexo 5)

Extracción de los datos

Para la obtención de los datos, y con la finalidad de facilitar el análisis, se diseñó una tabla de recogida de datos en la que se introdujeron los datos de variables de cada estudio como son el tamaño de la muestra, terapia aplicada, número de mujeres y hombres, dolor inicial y final, entre otras, además de la puntuación obtenida por la escala JADAD (Anexo 6).

La escala JADAD es una herramienta creada en 1996 por Alejandro R. Jadad y colaboradores cuya finalidad es la medición de la calidad de las publicaciones sobre ensayos clínicos que median el alivio del dolor (150). Esta escala se compone de 3 ítems a los cuales se les otorga una puntuación en función de su cumplimiento o no, teniendo como máximo 5 puntos y como mínimo 0 puntos. Los estudios cuya puntuación obtenida fueran inferior a 3 se consideraban estudios de baja calidad, por lo que automáticamente eran descartados para la inclusión en nuestro análisis estadístico del meta-análisis (150,151). (Anexo 7)

Además de este proceso de extracción, se diseñaron otras 2 tablas de recogida de datos (una para el grupo experimental y otra para grupo control) en las cuales figuraban los datos propios del estudio que se incluía, tipo de estudio, dosis (en el caso que fueran diversos tipos de dosis las estudiadas), tamaño muestral, dolor inicial y dolor final (expresados con la desviación estándar (SD) correspondiente). La finalidad de esta segunda extracción de datos fue facilitar el manejo estadístico de los mismos a la hora de realizar las pruebas estadísticas correspondientes que en próximas páginas se detallarán.

Evaluación del riesgo de sesgo para los estudios incluidos

Para la evaluación del riesgo de sesgo de los estudios se siguieron las indicaciones del Manual Cochrane Versión 5.1.0. A través de ella podemos analizar el riesgo de sesgo que tienen los artículos por sí mismos y el riesgo de sesgo que hay entre ellos (152).

En estos casos, cuando hablamos de sesgos, según el manual Cochrane podemos evaluar principalmente hasta 6 tipos de sesgos diferentes:

a. *Sesgo de selección*: hace referencia a la existencia o no de aleatorización en los grupos estudiados, así como en la existencia de la generación de la secuencia de las intervenciones a realizar. También hace referencia al proceso de ocultación de la secuencia por parte del personal que participa en este proceso inicial de reclutamiento.

b. *Sesgo de realización*: hace referencia a la presencia de cegamiento por parte de los participantes y personal del estudio en las intervenciones realizadas.

c. *Sesgo de detección*: hace referencia al proceso de cegamiento de los evaluadores para evitar el conocimiento de la intervención que se había aplicado.

d. *Sesgo de desgaste*: hace referencia a situaciones en las que los datos sobre los resultados obtenidos no están disponibles debido al abandono del estudio por parte del participante o a la existencia de datos incompletos.

e. *Sesgo de notificación*: hace referencia a la existencia de datos publicados selectivamente, evitando publicar los datos con menor valor significativo. Comúnmente es también conocido como "sesgo de publicación dentro del estudio".

f. *Otros sesgos*: hace referencia a fuentes de sesgos relevantes en ciertas ocasiones y que se pueden encontrar en algunos tipos de estudios determinados, como pueden ser por ejemplo intervenciones mezcladas entre grupo experimental y grupo control en el caso de combinar fármacos entre los participantes.

Para el análisis de riesgo de sesgo de los estudios incluidos se utilizó una herramienta informática proporcionada por Cochrane llamada Review Manager (RevMan). En concreto se utilizó la versión RevMan 5.3, en la cual se introdujo manualmente todos los datos de los estudios a incluir en el meta-análisis para su

posterior análisis de sesgos dentro de la aplicación y la elaboración final de las diferentes tablas de resumen.

En dichas tablas los datos obtenidos en función del tipo de sesgo analizado aparecen en tres colores diferentes que determinan lo siguiente:

- Color verde: riesgo bajo de sesgo.
- Color amarillo: riesgo de sesgo no determinado.
- Color rojo: riesgo alto de sesgo.

Las tablas generadas por esta herramienta informática corresponden a dos tipos:

1- *Gráfico del Riesgo de Sesgo:* ilustra la proporción de estudios con cada una de sus evaluaciones (Bajo riesgo, Alto riesgo, Riesgo poco claro)

2- *Resumen del Riesgo de Sesgo*: analiza las evaluaciones individualizadas por cada artículo incluido.

Análisis estadístico de los resultados obtenidos

Los datos estadísticos fueron analizados a través del software SSPS 25.0 detallándose para el análisis descriptivo la muestra total atendiendo a edad, duración de DM, duración de neuropatía, dolor principio y dolor final. Las variables numéricas (cuantitativas) se resumieron con medias y desviaciones típicas, o en caso de distribuciones asimétricas, mediante medianas y percentiles (P25 y P75).

Se realizaron pruebas no paramétricas para dos muestras independientes (U de Man-Withney) para comprobar la heterogeneidad de dos muestras ordinales, rechazándose la hipótesis nula (H_0) al obtenerse un valor de significación inferior a 0.05.

Para el análisis e interpretación de los datos de los estudios seleccionados, se calculó el promedio de los resultados de dolor final, así como el tamaño del efecto de cada uno de los estudios, y medidas de tendencia central y de dispersión. La

desviación típica es el elemento estadístico que toma en cuenta ambos componentes, lo que permite ponderar adecuadamente el peso de cada estudio que ingresa en el meta-análisis, por ello, se considera como criterio de inclusión que tenga el valor medio y el de la desviación típica para el dolor final, tanto en el grupo experimental como en el grupo placebo.

Se calculó el tamaño del efecto por cada uno de los artículos seleccionados, así como el tamaño del efecto global para cada uno de los tipos de tratamiento. La g de Hedges es una medida estandarizada del tamaño del efecto, que permite que se puedan comparar evaluaciones realizadas con distintas pruebas y escalas. Esta medida del tamaño del efecto no dice cuántas desviaciones típicas mide el efecto. La interpretación del tamaño del efecto se realiza de la siguiente forma:

- g de Hedges 0-0,5: tamaño del efecto pequeño
- g de Hedges 0,5 – 0,8: tamaño del efecto mediano
- g de Hedges > 0.8: tamaño del efecto grande

Se utilizó el gráfico forest plot para realizar la representación gráfica de los intervalos de confianza de los valores del tamaño del efecto. Se interpretó de tal forma que los valores positivos indican una mejoría del dolor. Todos aquellos intervalos de confianza que incluyan el cero, no se consideraron significativos en la mejoría del dolor.

RESULTADOS

Proceso de selección de los estudios

Como resultado del proceso de selección de los estudios, a continuación se muestra el diagrama de flujo correspondiente a los estudios finalmente incluidos (Figura 5), el cual ha sido basado en el diagrama de flujo proporcionado por la declaración PRISMA (149).
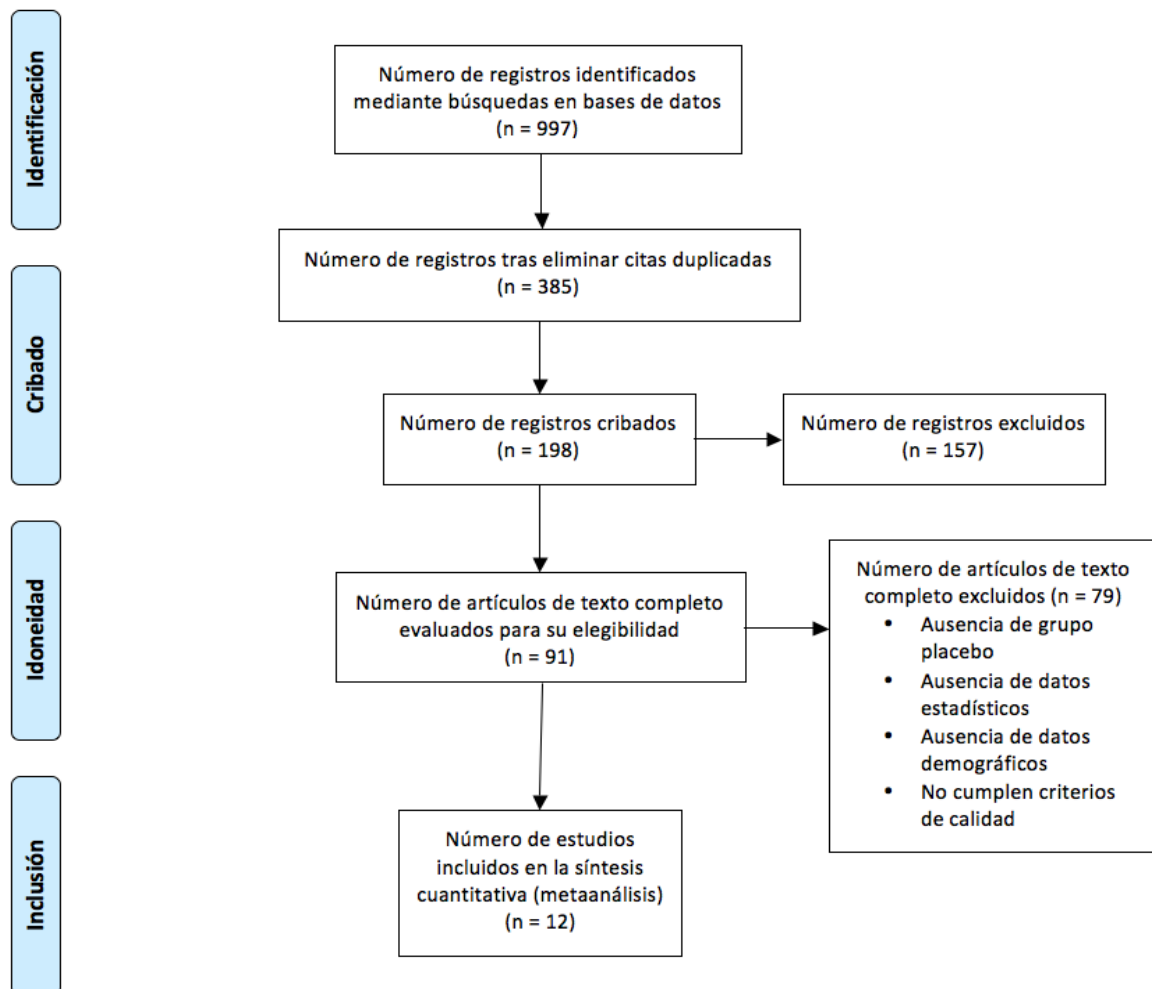

Figura 5: Diagrama de flujo de los estudios incluidos

Riesgo de sesgo de los estudios incluidos

En las figuras 6 y 7 se muestran los resultados del análisis de la evaluación del riesgo de sesgo de los estudios incluidos en el meta-análisis, concretamente se muestran el *Gráfico del Riesgo de Sesgo* y el *Resumen del Riesgo de Sesgo* respectivamente. En la figura 6 se aprecia el porcentaje, del total de los artículos incluidos, del riesgo de los diferentes tipos de sesgos, donde el mayor porcentaje de riesgo bajo de sesgo corresponde al sesgo de selección y al sesgo de notificación, y un porcentaje pequeño de alto riesgo de sesgo al cegamiento de participantes y personal. La figura 7 muestra el nivel de riesgo obtenido en cada uno de los sesgos analizados por cada artículo incluido de forma individualizada.
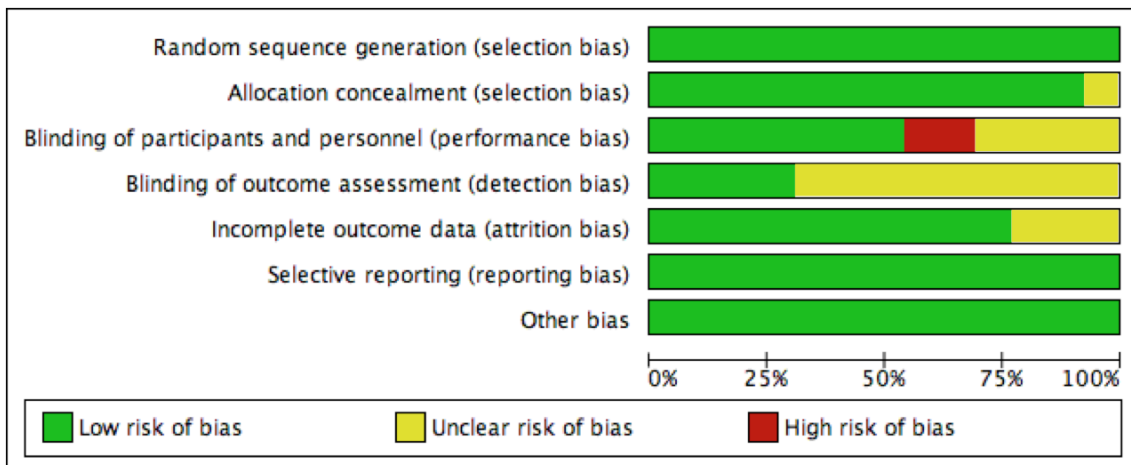

Figura 6: Gráfico del riesgo de sesgo de los estudios incluidos
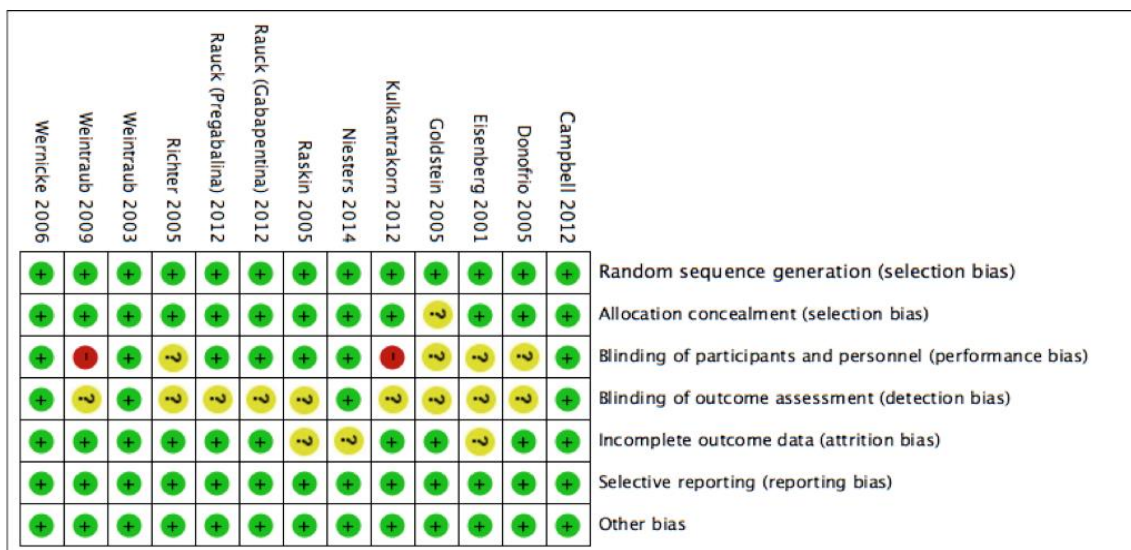

Figura 7: Resumen del riesgo de sesgo de los estudios incluidos

Características principales de los estudios incluidos

A continuación se presentan detalladamente, y organizado según tipo de terapia, las características de los estudios incluidos tras el proceso de selección, así como los datos necesarios para el análisis estadístico realizado. Estos datos fueron recogidos mediante tablas de recogida de datos cuyo formato se puede consultar en el anexo 6.

Terapias farmacológicas

- ***Eisenberg y colaboradores, 2001*** (153)***:***

ECA unicéntrico, doble ciego y con grupo control sobre lamotrigina a dosis máxima de 400 mg/día, de 6 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Goldstein y colaboradores, 2005*** (154)***:***

ECA multicéntrico, doble ciego y con grupo control sobre duloxetina a dosis de 20, 60 y 120 mg/día, de 12 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Raskin y colaboradores, 2005*** (155)***:***

ECA multicéntrico, doble ciego y con grupo control sobre duloxetina a dosis de 60 y 120 mg/día, de 12 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Richter y colaboradores, 2005*** (156)***:***

ECA multicéntrico, doble ciego y con grupo control sobre pregabalina a dosis de 150 y 600 mg/día, de 6 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Donofrio y colaboradores, 2005*** (157)***:***

Estudio abierto de extensión del ECA multicéntrico, doble ciego y con grupo control publicado por Raskin y colaboradores en 2004 (158), donde se muestran

los resultados totales de ambos estudios en los que se analiza el fármaco topiramato a dosis máxima de 600 mg/día durante un periodo total de 38 semanas. Según escala JADAD se obtiene una puntuación de 4.

- ***Wernicke y colaboradores, 2006*** (159)***:***

ECA multicéntrico, doble ciego y con grupo control sobre duloxetina a dosis de 60 y 120 mg/día, de 12 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Rauck y colaboradores, 2013*** (160)***:***

ECA multicéntrico, doble ciego y con grupo control sobre pregabalina y gabapentina a dosis de 300 mg/día y 1200, 2400, 3600 mg/día respectivamente, de 20 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

- ***Niesters y colaboradores, 2014*** (161)***:***

ECA unicéntrico, doble ciego y con grupo control sobre tapentadol a dosis máxima de 500 mg/día, de 4 semanas de duración. Según escala JADAD se obtiene una puntuación de 5.

Terapias tópicas

- ***Campbell y colaboradores, 2012*** (162)***:***

ECA multicéntrico, doble ciego y con grupo control sobre clonidina 0,1%, de 12 semanas de duración. Los pacientes se aplican 3,9 mg de gel al día. Según escala JADAD se obtiene una puntuación de 5.

- ***Kulkantrakorn y colaboradores, 2013*** (163)***:***

ECA unicéntrico, grupos cruzados, doble ciego y con grupo control sobre capsaicina 0,025%, de 8 semanas de duración. Los pacientes se aplican dos dosis de gel 3 – 4 veces al día. Al ser un estudio de grupos cruzados se decide incluir en el meta-análisis solamente la primera fase del estudio, evitando el cruce de los grupos. Según escala JADAD se obtiene una puntuación de 5.

Terapias físicas

- ***Weintraub colaboradores, 2003*** (62)***:***

ECA multicéntrico, doble ciego y con grupo control sobre magnetoterapia estática, de 4 meses de duración. La aplicación de la magnetoterapia estática se basó en la utilización de plantillas magnetizadas (en el caso del grupo placebo se utilizaron plantillas similares pero sin magnetizar) en el calzado de los pacientes durante el periodo completo del estudio. Según escala JADAD se obtiene una puntuación de 5.

- ***Weintraub y colaboradores, 2009*** (61)***:***

ECA multicéntrico, doble ciego y con grupo control sobre magnetoterapia pulsada, de 3 meses de duración. La aplicación de la magnetoterapia pulsada se realiza mediante sesiones divididas de 10 a 30 minutos (máximo 2 horas diarias) en los pies durante el periodo completo del estudio. Según escala JADAD se obtiene una puntuación de 5.

Todos los datos necesarios para el análisis estadístico obtenidos de los artículos se incluyeron en las tablas de recogida de datos, cuyo resultado se muestra en las tablas 8, 9 y 10.

TERAPIAS FARMACOLÓGICAS ORALES										
ESTUDIO	TRATAMIENTO	N	EDAD MEDIA (Años)	HOMBRES	MUJERES	DURACIÓN DIABETES (Años)	DURACIÓN NEUROPATÍA (Años)	DOLOR INICIAL	DOLOR FINAL	JADAD
GABAPENTINA Rauck 2013	1200 mg/día	62	57.5 (10.32)	34	28	-	-	6.64 (1.47)	4.09 (2.535)	5
	2400 mg/día	56	60.8 (8.97)	37	19	-	-	6.26 (1.22)	4.36 (2.049)	
	3600 mg/día	116	57.5 (9.87)	71	45	-	-	6.48 (1.43)	3.94 (2.423)	
	Placebo	120	60.1 (10.63)	73	47	-	-	6.49 (1.26)	4.4 (2.069)	
	TOTAL	354	58.7 (10.20)	215	139	-	-	-	-	
PREGABALINA Rauck 2013	300 mg/día	66	57.7 (10.59)	34	32	-	-	6.51 (1.27)	4.85 (1.833)	5
	Placebo	120	60.1 (10.63)	73	47	-	-	6.49 (1.26)	4.4 (2.069)	
	TOTAL	186	58.7 (10.20)	107	79	-	-	-	-	

ESTUDIO	TRATAMIENTO	N	EDAD MEDIA (Años)	HOMBRES	MUJERES	DURACIÓN DIABETES (Años)	DURACIÓN NEUROPATÍA (Años)	DOLOR INICIAL	DOLOR FINAL	JADAD
PREGABALINA **Richter 2005**	150 mg/día	79	56.3 +/- 9.4	57	22	8.2 +/- 9.1	-	6.5 +/- 1.3	4.9 +/- 2.2	5
	600 mg/día	82	57.8 +/- 9.5	46	36	9.3 +/- 8.8	-	6.7 +/- 1.7	4.3 +/- 2.7	
	Placebo	85	57.1 +/- 10.3	46	39	10.6 +/- 8.3	-	6.9 +/- 1.6	5.8 +/- 2.2	
	TOTAL	246	57.06	149	97	-	-	-	-	
DULOXETINA **Raskin 2005**	60 mg/día	116	58.3 (10.9)	48	68	14.6 (8.9)	4.5 (4.4)	5.5 (1.1)	3.0 (0.18)	5
	120 mg/día	116	59.0 (9.6)	61	55	13.9 (9.7)	4.5 (4.6)	5.7 (1.3)	3.23 (0.18)	
	Placebo	116	59.2 (9.8)	53	63	12.8 (8.6)	4.0 (3.5)	5.5 (1.3)	3.9 (0.18)	
	TOTAL	348	58.8 (10.1)	162	186	13.8 (9.1)	4.3 (4.2)	-	-	

ESTUDIO	TRATAMIENTO	N	EDAD MEDIA (Años)	HOMBRES	MUJERES	DURACIÓN DIABETES (Años)	DURACIÓN NEUROPATÍA (Años)	DOLOR INICIAL	DOLOR FINAL	JADAD
DULOXETINA **Goldstein 2005**	20 mg/día	115	60.3 (10.9)	75	40	12.1 (9.5)	3.7 (3.7)	5.9 (1.6)	3.54 (0.21)	5
	60 mg/día	114	59.2 (11.6)	79	35	11.4 (8.2)	3.8 (4.4)	6.0 (1.7)	3.11 (0.22)	
	120 mg/día	113	60.5 (10.8)	68	45	10.1 (9.0)	3.5 (2.8)	5.9 (1.4)	2.66 (0.23)	
	Placebo	115	60.4 (10.5)	59	56	11.4 (11.3)	4.0 (4.1)	5.8 (1.5)	3.89 (0.22)	
	TOTAL	457	60.1 (10.9)	281	176	11.3 (9.6)	3.7 (3.8)	-	-	
DULOXETINA **Wernicke 2006**	60 mg/día	114	59.7 (11.2)	74	40	9.7 (9.6)	3.6 (3.5)	6.1 (1.6)	3.38 (0.22)	5
	120 mg/día	112	61.5 (9.9)	61	51	9.9 (10.0)	4.4 (5.9)	6.2 (1.5)	3.36 (0.23)	
	Placebo	108	60.8 (10.6)	69	39	11.1 (9.1)	3.5 (3.2)	5.9 (1.4)	4.51 (0.23)	
	TOTAL	334	60.7 (10.6)	204	130	10.2 (9.6)	3.8 (4.4)	-	-	

ESTUDIO	TRATAMIENTO	N	EDAD MEDIA (Años)	HOMBRES	MUJERES	DURACIÓN DIABETES (Años)	DURACIÓN NEUROPATÍA (Años)	DOLOR INICIAL	DOLOR FINAL	JADAD
TOPIRAMATO **Donofrio 2005**	400 mg/día	117	59.4 (9.9)	59	58	10.1 (7.3)	3.4 (2.5)	6.76 (1.37)	2.80 (2.70)	4
	Placebo	86	59.1 (10.0)	47	39	10.5 (8.5)	3.2 (3.4)	6.60 (1.45)	3.55 (2.84)	
	TOTAL	203	59.2	106	97	-	-	-	-	
TAPENTADOL **Niesters 2014**	500 mg/día	12	63	7	5	12	6	6.5 (0.6)	3.9 (0.6)	5
	Placebo	12	64	7	5	11	6.5	6.5 (0.6)	4.8 (0.7)	
	TOTAL	24	63.5	14	10	-	-	-	-	
LAMOTRIGINA **Eisenberg 2001**	400 mg/día	27	52.7 +/- 2.1	17	10	13.9 +/- 1.7	3.6 +/- 0.7	6.4 +/- 0.1	4.2 +/- 0.1	5
	Placebo	26	57.8 +/- 1.7	16	10	9.6 +/- 1.1	3.8 +/- 0.6	6.6 +/- 0.1	5.3 +/- 0.1	
	TOTAL	53	-	33	20	-	-	-	-	

Tabla 8: Tabla de datos obtenidos de las terapias farmacológicas orales

TERAPIAS TÓPICAS										
ESTUDIO	TRATAMIENTO	N	EDAD MEDIA (Años)	HOMBRES	MUJERES	DURACIÓN DIABETES (Años)	DURACIÓN NEUROPATÍA (Años)	DOLOR INICIAL	DOLOR FINAL	JADAD
CAPSAICINA Kulkantrakorn	Capsaicina 0.025%	17		-	-		-	4.41 +/- 2.49	2.88 +/- 2.18	5
	Placebo	17		-	-		-	5.0 +/- 2.93	3.46 +/- 2.89	
	TOTAL	34	57.96	16	17	11.17 +/- 7.46	4.73 +/- 5.13	-	-	
CLONIDINA Campbell	Clonidina 0.1%	90		-	-		-			5
	Placebo	90		-	-		-	6.4 (1.4)	4.7 (1.9)	
	TOTAL	180	58.5	86	93	-	-	6.5 (1.5)	4.2 (2.2)	

Tabla 9: Tabla de datos obtenidos de las terapias tópicas

TERAPIAS FÍSICAS										
ESTUDIO	**TRATAMIENTO**	**N**	**EDAD MEDIA (Años)**	**HOMBRES**	**MUJERES**	**DURACIÓN DIABETES (Años)**	**DURACIÓN NEUROPATÍA (Años)**	**DOLOR INICIAL**	**DOLOR FINAL**	**JADAD**
MAGNETOTERAPIA Weintraub 2003	Magnetoterapia estática	141	62.6 +/- 11.3	-	-	13.0 +/- 10.8	-	5.8 +/- 2.3	4.1 +/- 2.7	5
	Placebo	118	63.2 +/- 11.2	-	-	11.6 +/- 10.2	-	5.8 +/- 2.3	4.3 +/- 2.8	
	TOTAL	259	62.9	135	124	-	-	-	-	
MAGNETOTERAPIA Weintraub 2009	Magnetoterapia pulsada	90	61.1 +/- 10.4	-	-	3.9 +/- 3.0	-	5.59 +/- 2.26	4.05 +/- 2.71	5
	Placebo	104	60.6 +/- 12.4	-	-	4.0 +/- 3.0	-	5.45 +/- 2.09	4.13 +/- 2.47	
	TOTAL	194	60.8	-	-	-	-	-	-	

Tabla 10: Tabla de datos obtenidos de las terapias físicas

Resultados del análisis estadístico

Análisis descriptivo

Con respecto a los resultados totales nos encontramos con una muestra total de pacientes incluidos en los estudios analizados de 2872, de los cuales 1755 corresponde a los pacientes incluidos en los grupos experimentales y 1117 a los incluidos en los grupos placebo. Para los pacientes incluidos en el grupo experimental se obtiene una edad media de 59,41 años, una duración media de diabetes de 10,85 años y una duración media de neuropatía de 3,86 años. A su vez los resultados en cuanto a dolor que se obtienen son de 6,12 sobre 10 en dolor inicial y 3,65 sobre 10 en dolor final. Para los pacientes incluidos en el grupo placebo se obtiene una edad media de 59,95 años, una duración media de diabetes de 10,26 años y una duración media de neuropatía de 3,64 años. Los resultados en cuanto a dolor que se obtienen determinan unas cifras de 6,10 sobre 10 en dolor inicial y 4,34 sobre 10 en dolor final. Los resultados detallados del análisis descriptivo se muestran las tablas 11, 12 y 13.

Tratamiento agrupado						
Grupo			Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
Experimental	Válido	Gabapentina	234	13,3	13,3	13,3
		Pregabalina	227	12,9	12,9	26,3
		Duloxetina	800	45,6	45,6	71,9
		Topiramato	117	6,7	6,7	78,5
		Tapentadol	12	,7	,7	79,2
		Lamotrigina	27	1,5	1,5	80,7
		Capsaicina 0,025%	17	1,0	1,0	81,7
		Clonidina 0,1%	90	5,1	5,1	86,8
		Magnoterapia	231	13,2	13,2	100,0
		Total	1755	100,0	100,0	
Placebo	Válido	Gabapentina	120	10,7	10,7	10,7
		Pregabalina	205	18,4	18,4	29,1

			Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
		Duloxetina	339	30,3	30,3	59,4
		Topiramato	86	7,7	7,7	67,1
		Tapentadol	12	1,1	1,1	68,2
		Lamotrigina	26	2,3	2,3	70,5
		Capsaicina 0,025%	17	1,5	1,5	72,1
		Clonidina 0,1%	90	8,1	8,1	80,1
		Magnoterapia	222	19,9	19,9	100,0
		Total	1117	100,0	100,0	

Tabla 11: Análisis descriptivo según tratamiento agrupado

Tipo de tratamiento						
Grupo			Frecuencia	Porcentaje	Porcentaje válido	Porcentaje acumulado
Experimental	Válido	Fármaco oral	1417	80,7	80,7	80,7
		Terapia física	231	13,2	13,2	93,9
		Fármaco tópico	107	6,1	6,1	100,0
		Total	1755	100,0	100,0	
Placebo	Válido	Fármaco oral	788	70,5	70,5	70,5
		Terapia física	222	19,9	19,9	90,4
		Fármaco tópico	107	9,6	9,6	100,0
		Total	1117	100,0	100,0	

Tabla 12: Análisis descriptivo según tipo de tratamiento

Estadísticos							
Grupo			Edad (en años)	Dolor principio	Dolor Final	Duración diabetes (en años)	Duración neuropatía o dolor neuropático (en años)
Experimental	N	Válido	1738	1755	1755	1438	1046
		Perdidos	17	0	0	317	709
	Media		59,4108	6,1238	3,6573	10,856	3,8608
	Desviación estándar		1,84004	,42351	,63592	2,5475	,53713
	Mínimo		52,70	4,41	2,66	3,9	3,00
	Máximo		63,00	6,76	4,90	14,6	6,00
	Percentiles	25	58,3000	5,8000	3,1100	9,700	3,5000
		50	59,4000	6,1000	3,5400	10,700	3,7000

			75	60,5000	6,5000	4,1000	13,000	4,4000
Placebo	N	Válido	1100	1117	1117	860	553
		Perdidos	17	0	0	257	564
	Media		59,9586	6,1018	4,3467	10,266	3,6438
	Desviación estándar		1,66011	,48312	,55248	2,4917	,59710
	Mínimo		57,10	5,00	3,46	4,0	2,90
	Máximo		64,00	6,90	5,80	12,8	6,50
	Percentiles	25	59,1000	5,8000	3,9000	9,600	3,2000
		50	60,1000	5,9000	4,4000	11,100	3,5000
		75	60,6000	6,4900	4,5100	11,600	4,0000

Tabla 13: Análisis descriptivo de los estadísticos resultantes por cada variable

Tras la realización de la prueba estadística U de Mann-Whitney para muestras independientes para el análisis de las hipótesis del estudio de investigación se obtienen los siguientes resultados reflejados en las figuras 8, 9, 10 y 11. En ellos se analizan las variables del estudio (dolor principio, dolor final, edad, duración diabetes y duración neuropatía) de forma global y por cada tipo de terapia.

En el contraste de hipótesis de resultados estadísticos globales se rechazan todas las hipótesis nulas, es decir, la distribución de las variables son diferentes entre las categorías de grupo.

En cuanto al contraste de hipótesis para las terapias orales, se acepta la hipótesis nula en la variable dolor principio, por lo que se entiende que en términos estadísticos el dolor principio en los grupos placebo y experimental es semejante. En el resto de variables se rechaza, por lo que su distribución es diferente en ambos grupos.

Para las terapias físicas se acepta la hipótesis nula en la variable edad, entendiéndose por ello que la edad de los individuos de cada grupo es similar. En el resto de variables se rechaza salvo en la duración de neuropatía o dolor neuropático, que es inviable calcular mediante métodos estadísticos.

En el contraste de hipótesis para las terapias tópicas los resultados son semejantes a los globales, por lo que se rechazan todas las hipótesis nulas y se determina que los datos de todas las variables son diferentes en los grupos estudiados.

Resumen de contrastes de hipótesis

	Hipótesis nula	Prueba	Sig.	Decisión
1	La distribución de Dolor principio es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
2	La distribución de Dolor Final es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
3	La distribución de Edad (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
4	La distribución de Duración diabetes (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,015	Rechace la hipótesis nula.
5	La distribución de Duración neuropatía o dolor neuropático (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.

Se muestran significaciones asintóticas. El nivel de significancia es ,05.

Figura 8: Contraste de hipótesis de resultados globales

Resumen de contrastes de hipótesis

	Hipótesis nula	Prueba	Sig.	Decisión
1	La distribución de Dolor principio es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,303	Conserve la hipótesis nula.
2	La distribución de Dolor Final es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
3	La distribución de Edad (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
4	La distribución de Duración diabetes (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
5	La distribución de Duración neuropatía o dolor neuropático (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.

Se muestran significaciones asintóticas. El nivel de significancia es ,05.

Figura 9: Contraste de hipótesis de terapias orales

Resumen de contrastes de hipótesis

	Hipótesis nula	Prueba	Sig.	Decisión
1	La distribución de Dolor principio es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
2	La distribución de Dolor Final es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
3	La distribución de Edad (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,229	Conserve la hipótesis nula.
4	La distribución de Duración diabetes (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
5	La distribución de Duración neuropatía o dolor neuropático (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	.	No se puede calcular.

Se muestran significaciones asintóticas. El nivel de significancia es ,05.

Figura 10: Contraste de hipótesis de terapias físicas

Resumen de contrastes de hipótesis

	Hipótesis nula	Prueba	Sig.	Decisión
1	La distribución de Dolor principio es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
2	La distribución de Dolor Final es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
3	La distribución de Edad (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
4	La distribución de Duración diabetes (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.
5	La distribución de Duración neuropatía o dolor neuropático (en años) es la misma entre las categorías de Grupo.	Prueba U de Mann-Whitney para muestras independientes	,000	Rechace la hipótesis nula.

Se muestran significaciones asintóticas. El nivel de significancia es ,05.

Figura 11: Contraste de hipótesis de terapias tópicas

Resultados meta-analíticos

Realizado el análisis estadístico para obtener el valor de la g de Hedges, en las tablas 14, 15 y 16 se muestran los resultados del mismo mediante el límite superior e inferior, p valor y el tamaño del efecto.

DOLOR FINAL	Hedges	Límite Inferior	Límite superior	p-valor	Tamaño del efecto
GABAPENTINA 1200 mg/día Rauck 2012	0,138	-0,188	0,463	ns	Sin efecto
GABAPENTINA 2400 mg/día Rauck 2012	0,019	-0,286	0,324	ns	Sin efecto
GABAPENTINA 3600 mg/día Rauck 2012	0,204	-0,083	0,491	ns	Sin efecto
PREGABALINA Rauck 2012	-0,225	-0,511	0,060	ns	Sin efecto
PREGABALINA 150 mg/día Richter 2005	0,407	0,070	0,744	<0,05	Pequeño
PREGABALINA 600 mg/día Richter 2005	0,607	0,235	0,980	<0,05	Mediano
DULOXETINA 60 mg/día Raskin 2005	4,984	4,961	5,007	<0,05	Grande
DULOXETINA 120 mg/día Raskin 2005	3,710	3,687	3,733	<0,05	Grande
DULOXETINA 20 mg/día Goldstein 2004	1,622	1,594	1,650	<0,05	Grande
DULOXETINA 60 mg/día Goldstein 2004	3,534	3,505	3,562	<0,05	Grande
DULOXETINA 120 mg/día Goldstein 2004	5,448	5,419	5,477	<0,05	Grande
DULOXETINA 60 mg/día Wernicke 2006	5,007	4,977	5,036	<0,05	Grande
DULOXETINA 120 mg/día Wernicke 2006	4,983	4,952	5,013	<0,05	Grande
TOPIRAMATO Donofrio 2005	0,271	-0,109	0,650	ns	Sin efecto
TAPENTADOL Niesters 2013	1,333	1,072	1,594	<0,05	Grande
LAMOTRIGINA Eisenberg 2001	10,837	10,811	10,864	<0,05	Grande
Tratamiento oral	**1,251**	**1,227**	**1,275**	**<0,05**	**Grande**

ns: No significativo, p-valor>0,05

Tabla 14: Análisis de g de Hedges en terapias orales

DOLOR FINAL	Hedges	Límite Inferior	Límite superior	p-valor	Tamaño del efecto
MAGNETOTERAPIA Weintraub 2009 **Magnetoterapia pulsada**	0,031	-0,333	0,394	ns	Sin efecto
MAGNETOTERAPIA Weintraub 2003 **Magnetoterapia estática**	0,073	-0,262	0,407	ns	Sin efecto
Tratamiento Físico	**0,052**	**-0,194**	**0,299**	**ns**	**Sin efecto**

ns: No significativo, p-valor>0,05

Tabla 15: Análisis de g de Hedges en terapias físicas

DOLOR FINAL	Hedges	Límite Inferior	Límite superior	p-valor	Tamaño del efecto
CAPSAICINA **Kulkantrakorn 2013**	0,221	-0,639	1,082	ns	Sin efecto
CLONIDINA **Campbell 2012**	0,242	-0,058	0,543	ns	Sin efecto
Tratamiento tópico	**0,238**	**-0,047**	**0,524**	**ns**	**Sin efecto**

ns: No significativo, p-valor>0,05

Tabla 16: Análisis de g de Hedges en terapias tópicas

Para la interpretación de los resultados se realiza representación gráfica mediante Forest Plot (Figura 11). Los valores positivos corresponden a los resultados a favor de la intervención y los resultados negativos a favor del control, siendo el 0 el punto nulo. Las líneas rojas corresponden al intervalo de confianza y su punto central a la media. Aquellos resultados cuyo intervalo de confianza crucen el 0 o punto nulo, se consideran como no significativos para el estudio. En la figura 11 las terapias físicas y tópicas no son significativas al cruzar el punto nulo, sin embargo, existen estudios dentro de las terapias farmacológicas orales que sí son significativas al existir una diferencia significativa a favor de la intervención.
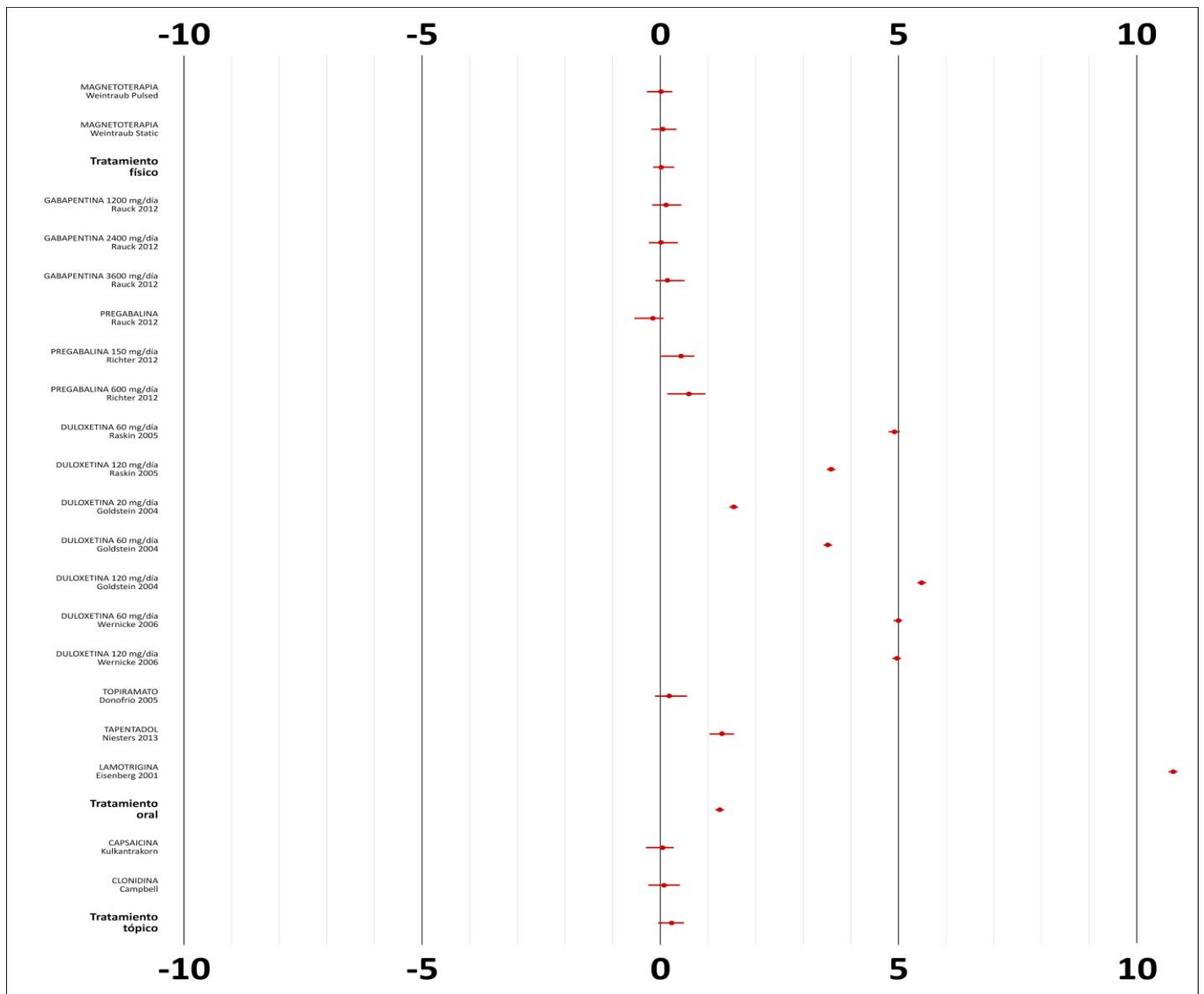
Figura 11: Forest Plot de los resultados obtenidos

DISCUSIÓN

La finalidad de este estudio fue analizar, a modo de meta-análisis, las diferentes alternativas terapéuticas existentes para el tratamiento de la neuropatía diabética dolorosa, con el fin principal de determinar cuales de ellas son las más efectivas en cuanto a alivio del dolor se refiere. Según los resultados analizados previamente nos encontramos con que, en términos estadísticos, las terapias físicas y tópicas analizadas no son significativas como para argumentar su uso, mientras que determinados tratamientos farmacológicos sí lo son.

Una vez terminado el análisis estadístico y la redacción de los resultados nos encontramos en disposición de poder valorar realmente los apartados principales de esta tesis y el fundamento de la realización del meta-análisis. Todos estos tratamientos que analizaremos a continuación vienen determinados por los objetivos marcados al principio del proceso, cuya finalidad es la consecución de los mismos.

A continuación se abordará la discusión a través de los resultados obtenidos mediante dos vertientes, considerándose por clase de terapia (ya sea física, tópica u oral) o por tipo de agente terapéutico. Todo este análisis se realizará en base al meta-análisis obtenido, la evidencia científica existente en la literatura, y la aplicabilidad de dichos tratamientos en el ámbito de las ciencias de la salud, teniendo siempre en cuenta que la finalidad de este estudio es determinar qué tipo de tratamiento es más efectivo para la neuropatía diabética dolorosa. Tras este análisis se desarrollarán diversos algoritmos de tratamientos que ayuden a los profesionales sanitarios en la toma de decisiones ante pacientes que presenten dicha patología.

Por ello, se procede al análisis a modo de discusión del estudio realizado, dividido en dos secciones:

Análisis por clase de terapia

Se analizan 3 clases de terapias como son las terapias farmacológicas orales, las terapias físicas y las terapias tópicas. De todos los artículos incluidos en ellas, y según los resultados obtenidos, determinamos que las terapias farmacológicas orales son las terapias realmente efectivas para el tratamiento de la NDD. Esta determinación coincide plenamente con las diversas guías de tratamiento y consensos existentes en la literatura científica como son NeuPSIG, NICE, EFNS, ADA, AAN, y AACE (13,14,30,48,69,140), en las que los mayores niveles de evidencia o las primeras líneas de tratamiento corresponden a farmacoterapia oral. En este sentido, el meta-análisis realizado reafirma y coincide en la terapia farmacológica oral como base en el tratamiento de la NDD al obtenerse un tamaño del efecto grande de los resultados obtenidos de los estudios incluidos.

Otros autores como Rosenborg y Watson realizaron una revisión sistemática de la literatura acerca de los tratamientos para la NDD donde encontraron como pilar básico el tratamiento farmacológico, considerando así mismo la posibilidad de combinar fármacos a la vez que otras terapias como son las terapias tópicas y físicas y terapias conductuales para conseguir aliviar de forma efectiva el dolor en estos pacientes (164). A su vez, Vinik y colaboradores realizaron una revisión donde analizan en profundidad todos los aspectos clínicos de las neuropatías diabéticas y determinan según su algoritmo realizado a las terapias farmacológicas como eje del tratamiento del dolor neuropático de origen diabético, coincidiendo a su vez con Rosenborg y Watson en la posibilidad de realizar combinaciones de fármacos u otras terapias para aumentar la efectividad en el alivio del dolor (165).

Con respecto a las terapias físicas y tópicas analizadas en su conjunto, los resultados estadísticos obtenidos muestran que son terapias sin efecto. Estos resultados no se pueden interpretar como una inefectividad en términos clínicos, ya que a pesar del pequeño volumen de estudios que se han podido incluir, existen diversas guías de las mencionadas anteriormente que incluyen estos tratamientos en sus análisis. En concreto, según la AAN (48), la capsaicina crema en su formato a 0,075% obtiene un nivel de recomendación B, y según la guía NICE (140) se

recomienda su utilización en dolor neuropático localizado cuando el paciente no tolere tratamiento farmacológico oral. A pesar de todo ello, la realidad de estos tipos de terapias tópicas y físicas es, en primer lugar, la escasa evidencia científica para su uso, catalogándose su análisis para capsaicina crema y clonidina crema como inconcluso según NeupSIG (30) o incluso no recomendándose la magnetoterapia por parte de la AAN (48), y en segundo lugar la falta de más revisiones sobre estos tipos de terapias. Las pocas revisiones que se encuentran sobre estas terapias para el dolor neuropático periférico y/o diabético demuestran, al igual que nuestros resultados obtenidos, la ineficacia de estas terapias y la dificultad para poder argumentar su uso debido a que la mayoría de los estudios incluidos para su análisis en dichas revisiones se consideran de baja calidad al tener ciertos problemas metodológicos, ya sea por deficiencias en el diseño del estudio, tamaño muestral pequeño, alto riesgo de sesgos entre otras limitaciones (12,15,166,167). Además, revisiones sistemáticas consideradas de mayor calidad como son las revisiones sistemáticas de Cochrane Library realizadas para el análisis de la efectividad de las terapias TENS, capsaicina a baja concentración y clonidina tópica para el dolor neuropático concluye, de forma muy similar a las revisiones mencionadas anteriormente. En el caso de TENS y capsaicina a baja concentración no existen criterios razonables para indicar su efectividad en el dolor neuropático de cualquier tipo (53,168), y para la clonidina tópica se puede llegar a recomendar, bajo un nivel de evidencia limitado, su uso como segunda línea para la NDD cuando no exista la posibilidad de aplicar otros tratamientos con mayor evidencia (169).

Análisis por tipo de agente terapéutico

a)   Gabapentina

Los resultados estadísticos del análisis del artículo incluido sobre gabapentina a cargo de Rauck y colaboradores (160) a dosis estudiadas de 1200, 2400 y 3600 mg/día respectivamente muestran un estudio sin tamaño del efecto (p-valor > 0,05). Sin embargo, el análisis propio del estudio refleja una reducción del dolor (diferencia de valor entre dolor final y dolor inicial) a dosis de 1200 mg/día y 3600

mg/día de 2.55 y 2.54 respectivamente, siendo dicha reducción de 1.90 para la dosis de 2400 mg/día.

Diversas guías clínicas y estudios de revisión coinciden en la eficacia de este fármaco ante esta patología, sin embargo el nivel de recomendación difiere en algunos casos, aunque siempre manteniendo la dosificación del medicamento desde dosis iniciales de 900 mg/día a un máximo de 3600 mg/día. Tanto para NeuPSIG, NICE, EFNS y AACE la gabapentina se encuentra como primera línea de tratamiento para la NDD, siendo para AAN y ADA un fármaco que debería usarse como segunda línea de tratamiento o con grado de recomendación nivel B. Estos datos son avalados a su vez por una revisión Cochrane realizada por Wiffen y colaboradores en 2017, siendo ésta una actualización de la ya realizada por los mismos autores en 2014 (170). Dicha revisión sistemática analizó la evidencia del uso de gabapentina en diversas condiciones de dolor neuropático, fundamentalmente en pacientes con NDD y neuralgia postherpética, para lo cual incluyeron 37 ensayos clínicos a doble ciego de dos semanas de duración como mínimo, comparando gabapentina (a dosis mínima de 1200 mg/día o superior) con placebo u otro tratamiento activo. Según sus resultados, existe un alto riesgo de sesgo en los estudios analizados debido principalmente al tamaño de la muestra, sin embargo, determinan que la gabapentina en dosis de 1800 mg/día a 3600 mg/día puede proveer un nivel óptimo de alivio del dolor en pacientes con NDD y neuralgia postherpética.

En términos de seguridad, la gabapentina es un fármaco incluido dentro del grupo de los antiepilépticos, con indicación para dolor neuropático periférico, y que como contraindicación única se encuentra la hipersensibilidad. Además de ello, hay que tener precaución con su uso en pacientes con insuficiencia renal o sometidos a hemodiálisis, y tener una vigilancia especial si aparecen reacciones anafilácticas, pensamientos e ideas suicidas, depresión respiratoria, o si el paciente presenta pancreatitis aguda o hace uso simultáneo de opioides (171).

Según todos estos datos analizados nos encontramos con un fármaco efectivo para el tratamiento de la NDD, cuya prescripción por parte de los profesionales de la

salud puede considerarse de carácter seguro siempre y cuando no se determinen las circunstancias detalladas anteriormente para su no aplicación, y por lo tanto pasa a formar parte a su vez del arsenal terapéutico a disposición del profesional sanitario para esta patología.

b) Pregabalina

Se incluyeron en nuestro estudio dos artículos sobre pregabalina a dosis estudiadas de 150, 300 y 600 mg/día (156,160), donde se obtiene estadísticamente un tamaño del efecto pequeño y mediano para el artículo donde se analizan las dosis a 150 y 600 mg/día, y sin efecto para el artículo que analiza la dosis a 300 mg/día. Los resultados obtenidos reflejan claramente cómo se trata de un fármaco eficaz para la NDD, datos que coinciden con las guías y revisiones de NeuPSIG, NICE, EFNS, AAN, AACE, y ADA donde la clasifican como el fármaco de primera recomendación con un nivel de eficacia A para el dolor neuropático crónico y/o NDD. Otras revisiones y/o meta-análisis realizados avalan también su uso como vía de primera elección para la NDD. Uno de estos estudios es el de Parsons y Li donde comparan la respuesta terapéutica de la pregabalina en pacientes con NDD moderada o severa a través de 11 ECAs con pregabalina a dosis flexible o fija de 150, 300 y 600 mg/día, concluyendo que la pregabalina es efectiva en pacientes con dolor severo y con dolor moderado, siendo aún más efectiva en aquellos con dolor severo (172). Arnold y colaboradores analizaron 14 ECAs de pregabalina a dosis fija para las patologías de NDD, neuralgia postherpética y fibromialgia, de donde destacan en sus resultados el beneficio de este fármaco en la NDD a dosis máxima de 300 mg/día (173). Derry y colaboradores, mediante revisión Cochrane, estudiaron la pregabalina en diversas condiciones de dolor neuropático, entre ellas la NDD, para lo cual analizaron 45 ensayos clínicos a doble ciego con 2 semanas de duración como mínimo y comparándola con placebo u otro tratamiento activo, de donde se concluye que la evidencia existente muestra la eficacia de la pregabalina para la NDD, neuralgia postherpética y dolor neuropático post-traumático mixto o sin clasificar (174).

La pregabalina, al igual que la gabapentina, es un fármaco del grupo de los antiepilépticos con indicación para el dolor neuropático periférico y central, que tiene como única contraindicación la hipersensibilidad al fármaco, y que se debe tener precaución en pacientes con problemas de insuficiencia renal e insuficiencia cardiaca. Además, este fármaco puede provocar alteraciones en la agudeza visual, somnolencia, visión borrosa, confusión, riesgo de pensamientos y comportamientos suicidas, y en administración con sustancias que provoquen estreñimiento puede disminuir la funcionalidad del tracto gastrointestinal inferior (175). A pesar de ello, la mayoría de las manifestaciones mencionadas anteriormente son comunes al uso de antiepilépticos, por lo que nos encontramos con un fármaco de uso seguro por los profesionales de la salud, los cuales podrán prescribirlo ante pacientes con NDD tras realizar una adecuada anamnesis sobre antecedentes médicos y tratamiento actual, y realizando una correcta educación al paciente sobre posibles efectos adversos que pueda producir el fármaco para actuar ante éstos en el caso de su aparición.

c) Duloxetina

Se analizan en el meta-análisis tres estudios sobre duloxetina a dosis correspondientes a 20, 60 y 120 mg/día, con resultados estadísticos positivos en cuanto a términos de eficacia se refiere, ya que los tres estudios obtienen un tamaño del efecto grande, por lo que se puede considerar, según los resultados obtenidos, un fármaco de alta eficacia para la NDD.

Estos datos estadísticos obtenidos coinciden en gran parte con las diversas guías y revisiones con las que se están comparando los resultados, ya que según NeuPSIG, NICE, EFNS, AACE y ADA obtiene un grado de recomendación A y se trataría de un fármaco de primera línea de uso. Sin embargo, para AAN la duloxetina pertenecería al grupo de los fármacos de recomendación nivel B. En una revisión sistemática de Cochrane a cargo de Lunn y colaboradores se concluye que hay una calidad de la evidencia moderada de los estudios incluidos sobre duloxetina en cuanto a alivio de dolor de las dosis estudiadas a 60 y 120 mg/día (176). Así mismo, otras revisiones ponen de manifiesto la eficacia de este fármaco frente a la

NDD: Hossain y colaboradores analizan mediante revisión sistemática 8 ECAs de alta calidad sobre duloxetina en pacientes con NDD, determinando el mayor efecto beneficioso de este fármaco frente al placebo (177); Rudroju y colaboradores realizaron un estudio para comparar efectividad, a modo de meta-análisis, entre 6 fármacos utilizados para el tratamiento de la NDD (amitriptilina, pregabalina, duloxetina, valproato, venlafaxina y gabapentina), de donde se concluye a través de los resultados obtenidos, que todos los tratamientos analizados tienen un efecto superior al placebo pero sin mostrar una superioridad entre los mismos, por lo que se determinada a su vez la efectividad de la duloxetina en esta patología (178); Sultan y colaboradores realizan una revisión sistemática de ECAs a doble ciego con placebo sobre duloxetina a 60 y 120 mg/día en pacientes con NDD y fibromialgia, de donde se obtienen 6 artículos, 3 de los cuales sobre NDD, y según los resultados obtenidos se concluye que la duloxetina es un fármaco eficaz para el tratamiento de la NDD (179).

Este fármaco está dentro del grupo de los antidepresivos, siendo en concreto un inhibidor de la recaptación de serotonina y noradrenalina. Sus contraindicaciones fundamentales se basan en la existencia de hipersensibilidad, enfermedad hepática que produzca insuficiencia hepática, insuficiencia renal grave, hipertensión arterial no controlada o en combinación con fármacos como los inhibidores de la monoamino oxidasa (IMAO), o como fluvoxamina, ciprofloxacino o enoxacino. Además, se debe tener especial precaución en pacientes que tomen anticoagulantes orales y/o medicamentos que afectan la función plaquetaria o en pacientes con riesgo elevado de hiponatremia (180). A pesar de ser un fármaco de gran eficacia frente a la NDD como se ha podido comprobar mediante nuestro estudio y las diversas revisiones y guías mencionadas que también lo han analizado, se concluye que es un fármaco con un elevado número de contraindicaciones y precauciones que deben hacer valorar a los profesionales de la salud su utilización de primera elección para la NDD frente a otros fármacos existentes, coincidiendo así con las recomendaciones de ADA. En el caso de su elección ante un paciente que presente NDD, se recomienda hacer un seguimiento más exhaustivo hacia ese paciente además de las medidas de educación al paciente ante la toma de fármacos de este tipo.

d) Topiramato

Los resultados obtenidos del meta-análisis realizado para el fármaco topiramato a dosis máxima de 400 mg/día muestran la ausencia del tamaño del efecto y la ausencia de significación estadística (g de Hedges: 0,271; p-valor > 0.05). Los datos propios del estudio muestran a su vez una reducción para el grupo experimental de 3,96 en cuanto a diferencia de dolor final con dolor inicial se refiere. Sin embargo, a la hora de analizar los resultados de dicho fármaco se encuentra que para NeuPSIG y EFNS los resultados obtenidos del análisis del topiramato son discrepantes o inconclusos, por lo que no recomiendan su uso. Al igual que nuestros resultados y las revisiones y guías mencionadas anteriormente, una revisión sistemática Cochrane a cargo de Wiffen y colaboradores donde analizaron ECAs a doble ciego con un periodo superior a dos semanas sobre topiramato en diversas condiciones de dolor neuropático crónico, concluye en no poder argumentar la eficacia del fármaco en NDD debido a los importantes sesgos que se incluían en los artículos analizados y al no existir diferencia significativa entre topiramato y placebo (181). De hecho, desde 2013 hasta la fecha actual no se encuentran en la literatura científica estudios de cierta relevancia donde se analice la eficacia de este fármaco en la NDD.

El topiramato es un fármaco que pertenece al grupo de los antiepilépticos cuyo uso común es para crisis epilépticas y migrañas (182), y pese a la existencia de estudios sobre su eficacia en la NDD, según la AEMPS no tiene indicación probada para el tratamiento de esta patología, por lo tanto, nos encontramos con un fármaco que debido a su ineficacia y la falta de indicación terapéutica no puede formar parte del arsenal terapéutico de los profesionales de la salud ante los pacientes que presenten NDD.

e) Tapentadol

Según el meta-análisis realizado a un artículo sobre tapentadol a dosis máxima de 500 mg/día se obtiene un tamaño del efecto grande, por lo que estamos ante un

fármaco de alta eficacia frente a la NDD. A pesar de que según nuestros resultados es un fármaco eficaz, la AAN considera que los resultados de sus análisis son inconclusos para este fármaco, y la guía EFNS lo encuadra en el grupo de opioides catalogándolo como recomendación de segunda y tercera línea y con resultados discrepantes. Además de ello, según las recomendaciones de ADA no se recomienda su uso debido al riesgo de adicción y otras complicaciones que derivan de este fármaco. Existen a su vez otras revisiones donde coinciden con nuestros resultados obtenidos al indicar los beneficios de esta terapia en cuanto a reducción del dolor en pacientes con NDD se refiere, como las llevadas a cabo por Schwartz y colaboradores que analizan dos estudios sobre el tratamiento mediante tapentadol en NDD a dosis de 100-220 mg dos veces al día(183), y Vadivelu y colaboradores que realizan una revisión sobre estudios clínicos acerca del mecanismo de acción del tapentadol y su eficacia clínica en la NDD (184).

Las reticencias en cuanto al uso de este fármaco radican en dos aspectos importantes:

- La escasez de estudios de cierta calidad que puedan llevar a análisis más certeros sobre la eficacia de este fármaco.

- Se trata de un fármaco perteneciente al grupo de los opioides, que no tiene indicación directa para la NDD pero si indirecta por su indicación para el dolor crónico en adultos, y que conlleva las contraindicaciones y complicaciones propias del grupo al que pertenece por la posibilidad de apariciones de hipersensibilidad, depresiones respiratorias, problemas gastrointestinales, interacciones farmacológicas y problemas de adicción entre otros (185).

Es por todo ello, que a pesar de haber obtenido buenos resultados según nuestro meta-análisis, para los profesionales de la salud debería considerarse como un fármaco de uso muy limitado, restringiéndolo a casos muy concretos en los que los pacientes no respondan a otros tratamientos de primera elección, y en cuyo caso también debería ser considerada la opción de remitirlo a unidades hospitalarias

donde puedan tener una estrecha vigilancia en cuanto a su uso y complicaciones se refiere.

f) Lamotrigina

Se incluye en el meta-análisis un artículo sobre lamotrigina a dosis máxima de 400 mg/día donde se obtiene, en términos estadísticos, un resultado relevante al obtener un tamaño del efecto grande. Sin embargo, al igual que ocurre de forma muy similar con el fármaco tapentadol, la AAN y la guía EFNS catalogan el análisis de este fármaco como inconcluso o con resultados discrepantes, siendo para la AAN un fármaco no recomendado. En cambio para la AECC seria un fármaco con grado de recomendación A por pertenecer al grupo de los anticonvulsionantes. También existe una revisión sistemática de Cochrane por Wiffen y colaboradores donde analizan este fármaco en el dolor neuropático crónico y la fibromialgia en adultos incluyendo 12 estudios, de los cuales 4 eran sobre NDD, y concluyendo según sus resultados que ninguno de los estudios incluidos aportó pruebas convincentes de la efectividad del fármaco para dolor neuropático crónico o fibromialgia a dosis diarias de 200 a 400 mg (186).

A pesar de los resultados discrepantes en términos de eficacia entre nuestro estudio y los demás estudios comparados, nos encontramos con un fármaco cuyas indicaciones concretas están basadas en el tratamiento de la epilepsia y la prevención de episodios depresivos en adolescentes mayores de 18 años con trastorno bipolar (187), por lo que no se podría considerar su presencia como alternativa terapéutica para la NDD para los profesionales de la salud.

g) Magnetoterapia

Se analizan dos estudios sobre magnetoterapia, tanto pulsada como estática, catalogándose sin efecto el análisis estadístico realizado (p-valor > 0.05). Las terapias físicas en el tratamiento de la NDD, como es el caso de la magnetoterapia, tienen menor influencia en la literatura científica debido a la escasez de estudios relevantes, ausencia de sesgos o calidad metodológica. Es por ello que, salvo las

recomendaciones de AAN donde su uso no está recomendado, el resto de guías y revisiones analizadas no incluyen estas terapias en sus estudios. Otras revisiones concluyen que este tipo de terapia no es efectiva en la NDD, como son la de Stein y colaboradores donde analizan mediante revisión sistemática y meta-análisis terapias eléctricas y electromagnéticas, de las cuales 4 pertenecen a ECAs comparados con placebo sin obtenerse mejoría significativa en el dolor neuropático en pacientes diabéticos, y la de Pieber y colaboradores, que realizaron una revisión sobre electroterapia en la NDD obteniendo resultados no satisfactorios para el uso de magnetoterapia ante esta patología (15,166). En casi la totalidad de las revisiones analizadas, coincidiendo a su vez con los datos obtenidos mediante nuestro meta-análisis, mantienen la ineficacia en cuanto a alivio del dolor se refiere o la imposibilidad de recomendación para esta patología por la falta de mayor cantidad de estudios con buena calidad metodológica, con mejor diseño y con ausencias de sesgos importantes, argumentando así la necesidad de un mayor número de ECAs con rigor metodológico (15,61,62,166).

Sin embargo, la escasez de efectos adversos de esta terapia unido a la capacitación del profesional de podología para el uso de terapias físicas en la practica clínica diaria, hace que la magnetoterapia pueda considerarse como una herramienta más para el tratamiento de la NDD, por la cual a su vez puedan desarrollarse estudios de investigación que avalen su eficacia en el ámbito podológico.

h) Capsaicina

A través del análisis estadístico realizado al artículo de capsaicina 0.025% incluido en el estudio se determina la ausencia de efecto según el estadístico g de Hedges. A pesar de los resultados obtenidos la capsaicina tópica en crema sí obtiene cierto grado de recomendación según NICE cuando el paciente no desee o tolere fármacos orales. Sin embargo, las revisiones de EFNS y AAN le otorgan un nivel de recomendación A/B y B respectivamente (en el caso de AAN se le otorga a la crema de capsaicina al 0.075%) por resultados discrepantes o ineficaces. En una revisión sistemática Cochrane realizada por Derry y Moore se analizaron 6 ECAs a doble ciego controlados por placebo por un periodo mínimo de 6 semanas utilizando

capsaicina a baja concentración (< 1%), llegando a la conclusión por parte de los autores que la capsaicina tópica a baja concentración carece de efecto significativo frente a otras cremas de tipo placebo, siendo esto debido a sesgos potenciales y tamaño muestral pequeño que tenían los estudios incluidos (44).

Pese a todo ello, la capsaicina tópica en forma de crema es un fármaco con indicación específica para la NDD y autorizado por la AEMPS, cuyos efectos adversos posibles son fundamentalmente la hipersensibilidad y la sensación de quemazón, y que pese a los resultados obtenidos en nuestro estudio, puede formar parte de las alternativas terapéuticas de los profesionales de la salud, y del profesional de podología en concreto, a la hora de abordar clínicamente a un paciente con NDD (188).

i) Clonidina

Según los resultados del meta-análisis realizado nos encontramos con el fármaco clonidina crema al 0,1% sin efecto según el estadístico g de Hedges. La clonidina tópica es un fármaco que ha sido analizado por NeuPSIG y EFNS catalogándose como inconcluso en el primer caso y con un nivel A/B de recomendación por ineficacia o resultados discrepantes en el segundo, coincidiendo de esa manera con nuestros resultados obtenidos. Se analiza también su eficacia mediante revisión sistemática Cochrane a cargo de Wrzosek y colaboradores a partir de 2 ECAs a doble ciego comparados con placebo u otro tratamiento activo de al menos dos semanas de duración, aplicando el gel de clonidina 0,1% sobre el área dolorosa 2 o 3 veces al día. En este estudio se concluye que en base a la limitada evidencia existente a cargo de pequeños estudios de calidad media – baja se puede determinar la existencia de beneficio con esta terapia en pacientes con NDD (169).

A pesar de que este fármaco tópico se encuentre en una situación similar a la capsaicina en cuanto a recomendaciones se refiere, en España no tiene indicación terapéutica para la NDD, por lo que no puede formar parte del arsenal terapéutico de los profesionales de la salud para el tratamiento de la NDD (189).

Aplicabilidad del estudio en la práctica clínica. Algoritmos de tratamiento

Una vez analizados todos los tratamientos incluidos en el meta-análisis y comparados con diversas revisiones y guías de práctica clínica de relevancia en el tratamiento de la NDD, nos disponemos a la realización de diversos algoritmos de tratamiento que sirvan como herramientas en el ámbito clínico a los profesionales de la salud, y en concreto a los profesionales de Podología, cuando se traten a pacientes con esta patología, siendo éste uno de los fundamentos principales del estudio. A continuación se muestran los algoritmos en función de la eficacia según nuestro estudio (figura 12) y las recomendaciones según el estudio realizado y los otros estudios comparados en función de su aplicabilidad clínica y seguridad (figura 13):
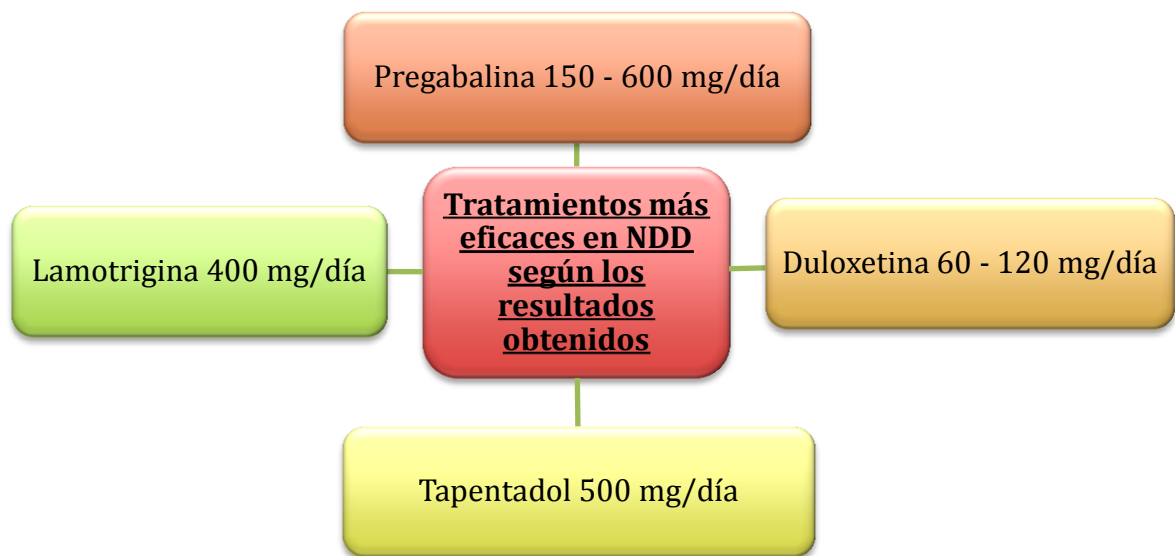
Figura 12: Propuesta de tratamiento según resultados obtenidos
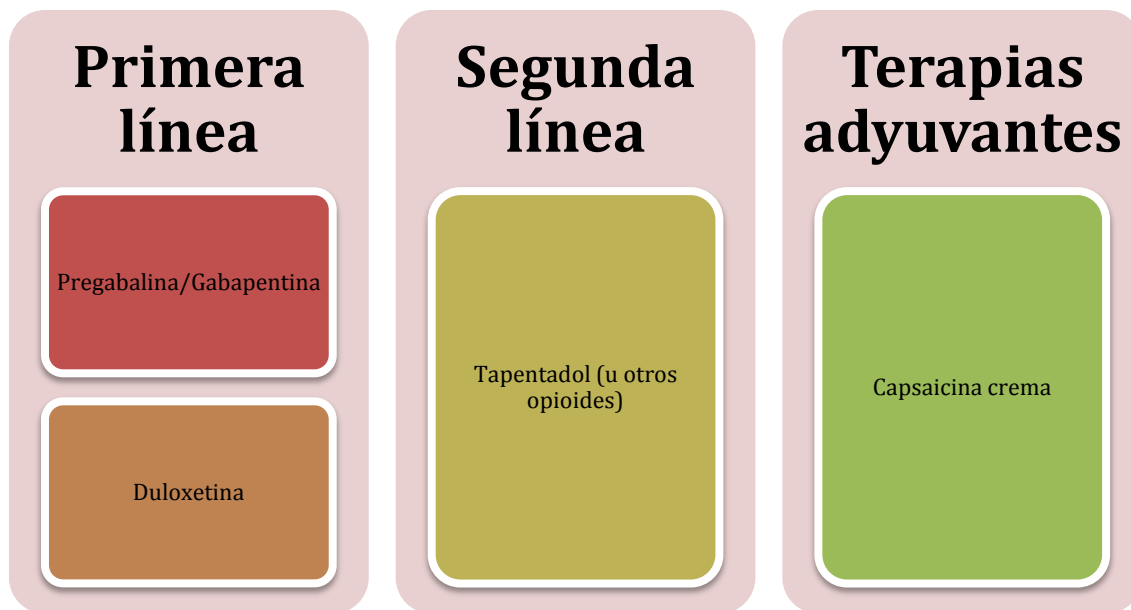
Figura 13: Propuesta de tratamiento según resultados combinados

Limitaciones

En el proceso de realización del estudio se han ido encontrando diversas limitaciones que han podido influir en la consecución final de ésta tesis. En este aspecto, las limitaciones fundamentales que se encontraron fueron la ausencia de datos estadísticos en gran cantidad de artículos seleccionados, por lo que fue imposible su inclusión para la realización del meta-análisis. Dicha dificultad intentó corregirse mediante el envío de correos electrónicos a los autores de los artículos que se encontraban en esa circunstancia, sin que hubiese respuesta alguna por parte de ninguno de ellos. A su vez, artículos potencialmente elegibles para el meta-análisis tuvieron que excluirse al no pasar la medida de calidad pertinente mediante la escala JADAD, por lo que el número de artículos finales disminuyó notablemente.

Otro aspecto importante a destacar en cuanto a limitación es la escasez de estudios de calidad en lo que a terapias físicas y tópicas se refiere, ya que la literatura científica existente es sensiblemente inferior si se compara con las terapias farmacológicas orales, lo que ha conllevado la inclusión de un número muy bajo de artículos que han podido ser seleccionados para el meta-análisis. Además, una gran cantidad de artículos existentes de todos los tipos de terapias analizaban el dolor

neuropático en general y no la NDD en particular, por lo que también tuvieron que ser descartados. El propósito fundamental de esta tesis ha sido analizar las alternativas terapéuticas para la NDD según tratamientos en monoterapia, es decir, no se aceptaban comparaciones entre fármacos o terapias combinadas, por lo que también esto ha generado un volumen pequeño de artículos incluidos finalmente. Por último, a este suceso se añade que gran cantidad de la literatura científica existente y accesible no es del todo reciente, es decir, gran cantidad de revisiones y artículos tienen más de 5 años de antigüedad, y no existen estudios y revisiones más actualizados que cumplieran los criterios de inclusión que se determinaron para esta tesis o con los que se pudieran realizar comparaciones.

CONCLUSIONES

1. Las terapias farmacológicas orales son las terapias más efectivas en el tratamiento de la NDD.

2. Los fármacos orales duloxetina, pregabalina, tapentadol y lamotrigina son los fármacos más eficaces para la NDD según el meta-análisis realizado.

3. Las terapias tópicas y físicas no son efectivas para la NDD según el meta-análisis realizado.

4. Las vías de primera elección para el tratamiento de la NDD, en términos de eficacia y aplicabilidad clínica según los resultados obtenidos y la evidencia científica existente, serían la pregabalina, gabapentina o duloxetina.

5. Las vías de segunda elección para el tratamiento de la NDD, en términos de eficacia y aplicabilidad clínica según los resultados obtenidos y la evidencia científica existente, serían el tapentadol u otros opiodes.

6. Según los resultados obtenidos y la evidencia científica existente la capsaicina tópica puede considerarse como una vía de tratamiento adyuvante cuando los pacientes no pueden o quieren tomar fármacos.

7. No se ha encontrado en la literatura científica argumentos suficientes para restringir el uso de fármacos orales en combinación con terapias físicas o tópicas.

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ÍNDICE DE ANEXOS

Anexo 1: Cuestionario ID-PAIN (82)

Cuestionario de Detección de Dolor Neuropático©

(Vesión española del cuestionario ID-PAIN© de Portenoy[16])

1. Por favor, responda a las siguientes preguntas sobre su dolor.

a. ¿Tiene dolor?	❏ Sí	❏ No
b. ¿Tiene algún dolor **aparte** de dolor de cabeza o migraña?	❏ Sí	❏ No

2. Señale en la figura las zonas donde le duele
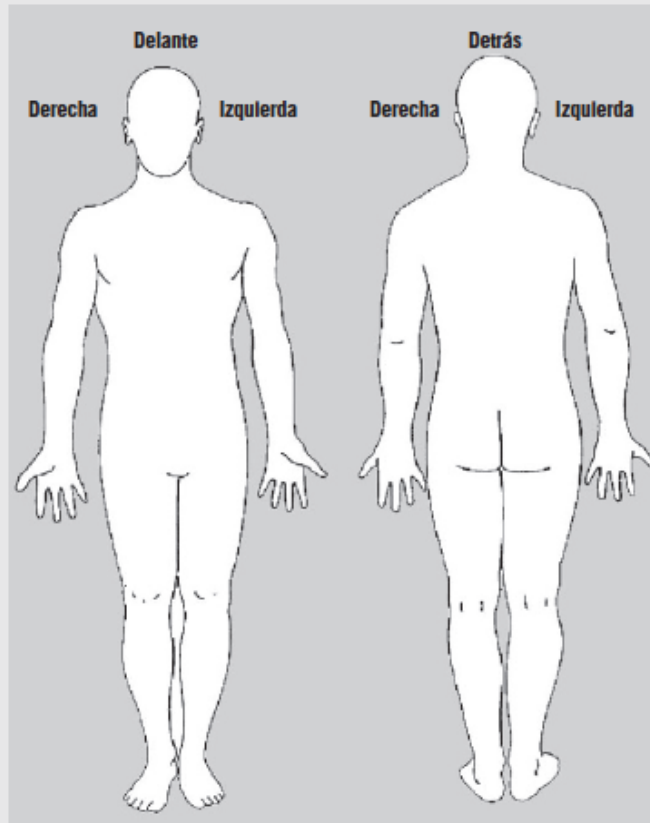
3. Marque **Sí** o **No** según haya sido su dolor en la última semana. Refiérase a las zonas marcadas en la figura anterior

a.	¿Ha notado el dolor como pinchazos?	❏ Sí	❏ No
b.	¿Ha notado el dolor como quemazón?	❏ Sí	❏ No
c.	¿Ha notado el dolor como acorchamiento?	❏ Sí	❏ No
d.	¿Ha notado el dolor como descargas eléctricas?	❏ Sí	❏ No
e.	¿Empeora el dolor con el roce de la ropa o las sábanas?	❏ Sí	❏ No
f.	¿El dolor es sólo en las articulaciones?	❏ Sí	❏ No

Muchas gracias por su colaboración

Anexo 2: Douleur Neuropathique en 4 questions (DN4) (84)

Cuestionario DN4
para la detección del Dolor Neuropático

CUESTIONARIO

Por favor, en las 4 preguntas de abajo, complete el cuestionario marcando una respuesta para cada número:

ENTREVISTA CON EL PACIENTE

Pregunta 1: ¿Tiene el dolor una o más de las siguientes características?

	Sí	No
1. Quemazón		
2. Sensación de frío doloroso		
3. Descargas eléctricas		

Pregunta 2: ¿Se asocia el dolor con uno o más de los siguientes síntomas en la misma zona?

	Sí	No
4. Hormigueo		
5. Sensación de alfileres y agujas		
6. Entumecimiento		
7. Picazón		

EXAMEN DEL PACIENTE

Pregunta 3: ¿Está el dolor localizado en una zona donde el examen físico puede mostrar una o más de las siguientes características?

	Sí	No
8. Hipoestesia al tacto		
9. Hipoestesia a los pinchazos		

Pregunta 4: En la zona dolorosa, el dolor puede ser causado o incrementado por:

	Sí	No
10. Cepillado		

Suma de todos los puntos positivos. Puntuación del paciente: /10

INTERPRETACIÓN: Se confirma el diagnóstico y se considera caso de estudio si la puntuación es mayor o igual a 3/10

Anexo 3: Escala LANSS (190)

LA ESCALA DE DOLOR DE LANSS
Evaluación de síntomas neuropáticos de Leeds

NOMBRE.. FECHA..

Esta escala del dolor puede ayudarnos a saber si los nervios que trasmiten sus señales de dolor están funcionando normalmente o no. Es importante saber eso por si se necesitan tratamientos diferentes para controlar el dolor que usted siente.

A. CUESTIONARIO SOBRE EL DOLOR

—Piense en *cómo ha sido su dolor en la última semana.*
—Por favor, indique si algunas de las siguientes descripciones se corresponden exactamente con el dolor que usted siente.

1. ¿Percibe el dolor como sensaciones extrañas y desagradables en su piel? Esas sensaciones podrían describirse con palabras como picazón, hormigueo, pinchazos y agujetas.

a) NO – El dolor que siento no se parece realmente a eso   (0)
b) SÍ – Tengo esas sensaciones con frecuencia   (5)

2. ¿Su dolor hace que la piel de la zona dolorida tenga un aspecto diferente al normal? Ese aspecto podría describirse con palabras como moteado o más rojo o rosa de lo normal.

a) NO – El dolor que siento no afecta realmente a mi piel   (0)
b) SÍ – He observado que el dolor hace que mi piel tenga un aspecto diferente
   al normal   (5)

3. ¿Hace su dolor que la piel afectada tenga una sensibilidad anormal al tacto? Esa sensibilidad anormal puede describirse como sensación desagradable ante ligeros toques de la piel, o dolor al usar ropa apretada.

a) NO – El dolor que siento no provoca una sensibilidad anormal de la piel en esa zona.   (0)
b) SÍ – Mi piel parece tener una sensibilidad anormal al tacto en esa zona.   (3)

4. ¿Aparece su dolor repentinamente y a ráfagas, sin razón aparente cuando está usted quieto? Esas sensaciones pueden describirse con palabras como descargas eléctricas, sobresalto y ráfaga.

a) NO – El dolor que siento no es realmente así.   (0)
b) SÍ – Tengo esas sensaciones bastante a menudo.   (2)

5. ¿Su dolor le hace sentir como si la temperatura de la piel en la zona dolorida hubiera cambiado de forma anormal? Esas sensaciones pueden describirse con palabras como calor y ardiente.

a) NO – En realidad no tengo esas sensaciones.   (0)
b) SÍ – Tengo esas sensaciones bastante a menudo.   (1)

B. EXPLORACIÓN SENSORIAL

La sensibilidad de la piel puede examinarse comparando la zona dolorida con una zona contralateral o adyacente no dolorida para determinar la presencia de alodinia y una alteración del umbral de pinchazo (UP).

1. ALODINIA

Se examina la respuesta a ligeros toques con un paño de algodón sobre la zona no dolorida y luego sobre la zona dolorida. En el caso de que se experimenten sensaciones normales en la zona no dolorida, pero sensaciones dolorosas o desagradables (hormigueo, náuseas) en la zona dolorida con los toques, existirá alodinia.

a) NO, sensación normal en las dos zonas. (0)
b) SÍ, alodinia sólo en la zona dolorida. (5)

2. UMBRAL DE PINCHAZO ALTERADO

Se determina el umbral de pinchazo comparando la respuesta a una aguja de calibre 23 (azul) acoplada al cilindro de una jeringa de 2 ml y colocada suavemente sobre la piel en una zona no dolorida y luego en una zona dolorida.

En el caso de que se sienta un pinchazo agudo en la zona no dolorida, pero una sensación diferente en la zona dolorida; p. ej., nada/sólo romo (UP elevado) o una sensación muy dolorosa (UP bajo), existirá una alteración del UP.

Si no se siente un pinchazo en ninguna de las dos zonas, se aumentará el peso de la jeringa y se repetirá el procedimiento.

a) NO, la misma sensación en las dos zonas. (0)
b) SÍ, un UP alterado en la zona dolorida. (3)

PUNTUACIÓN:

Se suman los valores entre paréntesis de la descripción sensorial y la exploración sensorial para obtener la puntuación total.

PUNTUACIÓN TOTAL (MÁXIMO 24) ....

Si la puntuación <12, es *poco probable* que mecanismos neuropáticos contribuyan al dolor del paciente.
Si la puntuación es ≥12, es *probable* que mecanismos neuropáticos contribuyan al dolor del paciente.

Anexo 4: Cuestionario PainDETECT (88)

painDETECT®   **CUESTIONARIO DEL DOLOR**

Fecha: ....   Paciente: Nombre: Apellidos:

¿Cómo valoraría el dolor que siente **ahora**, en este momento?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Ningún dolor — Máximo dolor

¿Cuál ha sido la intensidad del dolor **más fuerte** que ha sentido en las últimas 4 semanas?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Ningún dolor — Máximo dolor

¿Por término medio, cuál ha sido la intensidad de su dolor en las últimas 4 semanas?

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Ningún dolor — Máximo dolor

Marque su principal zona de dolor

Marque con una cruz la imagen que mejor describa el curso de su dolor:

Dolor constante con ligeras fluctuaciones ☐

Dolor constante con ataques de dolor ☐

Ataques de dolor sin dolor entre los ataques ☐

Ataques de dolor frecuentes con dolor entre los ataques ☐

¿Se irradia el dolor hacia otras partes de su cuerpo?   sí ☐   no ☐
Si la respuesta es sí, indique con una flecha la dirección hacia la que se irradia el dolor.

¿Tiene una sensación de quemazón (p.ej. como por roce de ortigas o al tocar la lejía) en la zona de dolor marcada?

no ☐   muy ligera ☐   ligera ☐   moderada ☐   intensa ☐   muy intensa ☐

¿Tiene una sensación de hormigueo o cosquilleo (como una corriente eléctrica) en la zona de dolor marcada?

no ☐   muy ligera ☐   ligera ☐   moderada ☐   intensa ☐   muy intensa ☐

¿Le produce dolor cualquier ligero roce (p.ej. la ropa o las sábanas) en esta zona?

no ☐   muy ligero ☐   ligero ☐   moderado ☐   intenso ☐   muy intenso ☐

¿Tiene ataques de dolor repentinos, como descargas eléctricas, en la zona de dolor marcada?

no ☐   muy ligeros ☐   ligeros ☐   moderados ☐   intensos ☐   muy intensos ☐

¿En alguna ocasión le produce dolor el contacto del frío o el calor (p.ej. el agua de la ducha) en esta zona?

no ☐   muy ligero ☐   ligeros ☐   moderado ☐   intenso ☐   muy intenso ☐

¿Tiene una sensación de entumecimiento (adormecimiento) en la zona de dolor marcada?

no ☐   muy ligera ☐   ligera ☐   moderada ☐   intensa ☐   muy intensa ☐

¿Se desencadena el dolor con solo una ligera presión en la zona de dolor marcada (p. ej. con el dedo)?

no ☐   muy ligero ☐   ligero ☐   moderado ☐   intenso ☐   muy intenso ☐

(a rellenar por el médico)

no	muy ligero	ligero	moderado	intenso	muy intenso
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐	☐ x 3 = ☐	☐ x 4 = ☐	☐ x 5 = ☐

Puntuación total ☐ sobre 35

116

painDETECT® — Puntuación del cuestionario del dolor

Fecha: .... Paciente: Nombre: .... Apellidos: ....

Transcriba la puntuación total del cuestionario del dolor:
Puntuación total ☐☐

Sume las siguientes cifras en función del patrón de comportamiento del dolor marcado y de la presencia o ausencia de dolor irradiado. A continuación calcule la puntuación final:

	Dolor constante con ligeras fluctuaciones	0	
	Dolor constante con ataques de dolor	-1	si se ha marcado esta imagen, o
	Ataques de dolor sin dolor entre los ataques	+1	si se ha marcado esta imagen, o
	Ataques de dolor frecuentes con dolor entre los ataques	+1	si se ha marcado esta imagen
	¿Dolor irradiado?	+2	si la respuesta es sí

Puntuación final ☐☐

Resultado del análisis
de la presencia de un componente de dolor neuropático

negativo	dudoso	positivo

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38

No es probable que exista un componente de dolor neuropático (< 15%)

El resultado es ambiguo, pero puede existir un componente de dolor neuropático

Es probable que exista un componente de dolor neuropático (> 90%)
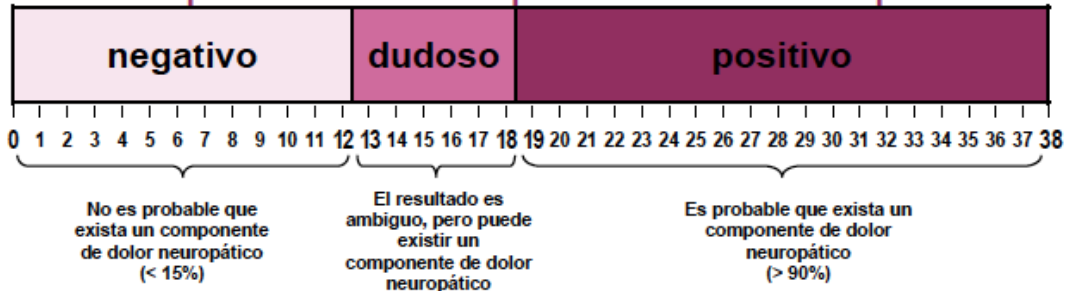
Anexo 5: E-mail enviado a autores de artículos potencialmente seleccionables

SAMUEL VILAR PALOMO
Mar 19/04/2016, 19:18
jwymer@upstateneurology.com

Dear Mr. Wymer

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called **"Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens",** because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I found the mean reduction in pain scale scores of the group Lacosamide 400mg/day (6.5 to 4.0), but I don´t find the mean reduction in pain scale scores of the group Lacosamide 200mg/day and Lacosamide 600mg/day.

Thanks so much.

Kind regards

Samuel Vilar Palomo
Coordinador Enfermeria Unidad del Dolor
Hospital Virgen del Rocío

SAMUEL VILAR PALOMO
Mar 19/04/2016, 18:59
ataher@aol.com

Dear Mr. Shaibani

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called "*Lacosamide in painful diabetic neuropathy: an 18-week double-blind placebo-controlled trial",* because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I found the mean reduction in pain scale scores of the group Lacosamide 400mg/day (6.4 to 3.9), but I don´t find the mean reduction in pain scale scores of the group Lacosamide 200mg/day (6.3 to … ¿?) and Lacosamide 600mg/day (6.3 to … ??).

Thanks so much.

Kind regards

Samuel Vilar Palomo

Coordinador Enfermería Unidad del Dolor
Hospital Virgen del Rocío

SAMUEL VILAR PALOMO
Mar 19/04/2016, 19:57
miwneuro@pol.net

Dear Mr. Weintraub

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called **"Pulsed electromagnetic fields to reduce diabetic neuropathic pain and stimulate neuronal repair: a randomized controlled trial",** because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I don´t find in the baseline demographics characteristics how many male/female are included (not in percentage)

Thanks so much.

Kind regards

Samuel Vilar Palomo
Coordinador Enfermería Unidad del Dolor
Hospital Virgen del Rocío

SAMUEL VILAR PALOMO
Mar 19/04/2016, 19:50
bosi.emanuele@hsr.it

Dear Mr. Bosi

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called **"Frequency-modulated electromagnetic neural stimulation (FREMS) as a treatment for symptomatic diabetic neuropathy: results from a double-blind, randomised, multicentre, long-term, placebo-controlled clinical trial",** because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I don´t find the mean reduction in pain scale scores of the Treatment group (31.6 to … ¿?) and Placebo group (40.9 to … ??).

Thanks so much.

Kind regards

Samuel Vilar Palomo
Coordinador Enfermería Unidad del Dolor
Hospital Virgen del Rocío

↩ ⤆ → ⋯

Dear Mr. Satoh

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called **"Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial",** because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I don´t find the mean reduction in pain scale scores of the group Pregabalin 300mg/day (6.0 to ... ??) and Pregabalin 600mg/day. (6.1 to ... ??)

Thanks so much.

Kind regards

Samuel Vilar Palomo
Coordinador Enfermeria Unidad del Dolor
Hospital Virgen del Rocío

↩ ⤆ → ⋯

Dear Mr. Mahoney

My name is Samuel Vilar, i´m the Nursing Coordinator of the Pain Unit in Hospital Virgen del Rocío from Seville (Spain).
I am contacting you regarding your article called **"Topical ketamine cream in the treatment of painful diabetic neuropathy: a randomized, placebo-controlled, double-blind initial study.",** because I am currently conducting a research study on neuropathic pain and would need, if possible and would be so kind, could give me the following information missing me.

- I don´t find the mean reduction in pain scale scores of the ketamine group and placebo group (numerical dates)

Thanks so much.

Kind regards

Samuel Vilar Palomo
Coordinador Enfermeria Unidad del Dolor
Hospital Virgen del Rocío

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Anexo 6: Tabla de recogida de datos

ESTUDIO	TRATAMIENTO	N	EDAD	HOMBRES	MUJERES	DURACION DIABETES	DURACION NEUROPATIA	DOLOR INICIAL	DOLOR FINAL	JADAD

Anexo 7: Escala JADAD (150)

Lea el artículo e intente responder las siguientes preguntas (consulte las instrucciones adjuntas):	
1. ¿Se describió el estudio como aleatorio (esto incluye el uso de palabras como randomizado, al azar y aleatorización)?	
2. ¿Se describió el estudio como doble ciego?	
3. ¿Hubo una descripción de los retiros y abandonos?	

Puntuación de los artículos: Otorgue una puntuación de 1 punto por cada "sí" o 0 puntos por cada "no". No hay puntos intermedios	
Dar un punto adicional si:	Para la pregunta 1, el método para generar la secuencia de aleatorización fue descrito y fue apropiado (tabla de números aleatorios, generados por computadora, etc.).
Y/o:	Si para la pregunta 2 el método de doble cegamiento era descrito y fue apropiado (placebo idéntico, placebo activo, dummy, etc.)
Deducir 1 punto si:	Para la pregunta 1, el método para generar la secuencia de aleatorización se describió y fue inapropiado (los pacientes fueron asignados alternativamente, o según la fecha de nacimiento, número de hospital, etc.)
Y/o:	Para la pregunta 2, el estudio fue descrito como doble ciego pero el método de cegamiento fue inadecuado. (p. ej., comparación de comprimidos versus inyección sin

	doble dummy)
Pautas para la evaluación	

1.   Aleatorización
Un método para generar la secuencia de aleatorización se considerará apropiado si permitió a cada participante del estudio tener las mismas posibilidades de recibir cada intervención y los investigadores no pudieron predecir qué tratamiento seguirían. Métodos de asignación utilizando La fecha de nacimiento, la fecha de ingreso, los números de hospital o la alternancia no deben considerarse apropiados.
2.   Doble cegamiento
Un estudio debe considerarse doble ciego si se utiliza la palabra "doble ciego". El método se considerará apropiado si se afirma que ni la persona que realiza las evaluaciones ni el participante del estudio pudo identificar la intervención que se está evaluando, o si en la ausencia de tal declaración, se menciona el uso de placebos activos, placebos idénticos o dummies.
3.   Retiros y abandonos.
Participantes que fueron incluidos en el estudio pero no completaron el período de observación o quienes no fueron incluidos en el análisis deben ser descritos. Hay que hacer constar el número y las razones para la retirada en cada grupo. Si no hubiera retiros, debería ser enunciado en el artículo. Si no hay una declaración sobre los retiros, este artículo no debe obtener puntos.

Anexo 8: Artículo publicado relacionado con la tesis doctoral

Therapeutic alternatives in painful diabetic neuropathy: a meta-analysis of randomized controlled trials

[1]Pain Clinic, University Hospital Virgen del Rocío, [2]Department of Nursing, Physiotherapy and Podiatry, University of Seville, [3]Department of Nursing, Physiotherapy and Podiatry, University Hospital Cruz Roja, Seville, Spain

Samuel Vilar[1], Jose Manuel Castillo[2], Pedro V. Munuera Martínez[2], María Reina[2], and Manuel Pabón[3]

Background: One of the most frequent problems caused by diabetes is the so called painful diabetic neuropathy. This condition can be treated through numerous types of therapy. The purpose of this study was to analyze, as a meta-analysis, different treatments used to alleviate painful diabetic neuropathy, with the aim of generating results that help making decisions when applying such treatments to tackle this pathology.

Methods: A search was conducted in the main databases for Health Sciences, such as PUBMED, Web of Science (WOS), and IME biomedicina (Spanish Medical Reports in Biomedicine), to gather randomized controlled trials about treatments used for painful diabetic neuropathy. The analyzed studies were required to meet the inclusion criteria selected, especially those results related to pain intensity.

Results: Nine randomized controlled trials were chosen. The meta-analysis shows significant positive effects for those treatments based on tapentadol [g: -1.333, 95% CI (-1.594; -1.072), $P < 0.05$], duloxetine [g: -1.622, 95 % CI (-1.650; -1.594), $P < 0.05$], pregabalin [g: -0.607, 95% CI (-0.980; -0.325), $P < 0.05$], and clonidine [g: -0.242, 95 % CI (-0.543; -0.058), $P < 0.05$].

Conclusions: This meta-analysis indicates the effectiveness of the treatments based on duloxetine, gabapentin and pregabalin, as well as other drugs, such as tapentadol and topic clonidine, whose use is better prescribed in more specific situations. The results provided can help increase the knowledge about the treatment of painful diabetic neuropathy and also in the making of clinical practice guidelines for healthcare professionals. **(Korean J Pain 2018; 31: 253-60)**

Key Words: Chronic pain; Diabetes complications; Diabetic neuropathies; Pain; Pain management; Pain unit.

INTRODUCTION

Diabetes is one of the most important and prevalent diseases in current society, with approximately 415 million people affected worldwide in 2015 and an estimate for the year 2040 of 642 million people [1]. Given the importance of this detail, one of the consequences of this disease must be highlighted, which is the diabetic foot, defined by the

WHO (World Health Organization) as "the presence of ulceration, infection and/or gangrene in the foot associated with diabetic neuropathy and different degrees of peripheral vascular disease as a consequence of the complex interaction of different factors induced by maintained hyperglycemia" [2].

One of the most frequent problems among the patients who suffer from this condition is neuropathic pain, which in scientific terminology is known as painful diabetic neuropathy. It was defined by Boulton et al. (2005) [3] as the "presence of symptoms and/or signs of peripheral nervous dysfunction in people with diabetes, after excluding other causes".

Painful diabetic neuropathy is treated through numerous therapeutic alternatives. The most common therapies are based on antidepressants, anticonvulsants, antipsychotics, opioids, local anesthetics and inhibitors of serotonin and noradrenaline reuptake, among others. In addition to these drugs, most of which are administered orally, there are other ways of application, also commonly used, such as patches or creams, as well as non-pharmacological treatments, as is the case of physical therapies [4-8].

All of the abovementioned motivated the realization of the present study, which analyzed, as a meta-analysis, different treatments used to alleviate painful diabetic neuropathy, with the aim of generating results that help making decisions when applying such treatments to tackle this pathology.

MATERIALS AND METHODS

This meta-analysis was conducted following the "Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)" guidelines [9].

1. Data sources

To obtain the data, a search in the main databases for Health Sciences, such as PUBMED, Web of Science (WOS) and IME biomedicina (Spanish Medical Reports in Biomedicine) was conducted, using the combination of the terms "pain", "painful diabetic neuropathy", "diabetic neuropathy", "neuropathic pain", "treatment", "therapy", "dolor neuropático", "dolor", "neuropatía diabética", "neuropatía diabética dolorosa", "tratamiento" and "terapia"

through the boolean operators AND and OR, and the use of truncations.

Example of full electronic search strategy for a database

PUBMED: "Painful diabetic neuropathy" AND (treatment OR therap*)

All the resulting articles, regardless of their publication date, were susceptible of inclusion in the study, until the final date of the search.

2. Selection of studies

All those randomized controlled trials that were accessible in full-text and met the inclusion criteria according to the PICO process (P: patient; I: intervention; C: comparison; O: outcomes) were included.

1. Patients: Patients over 18 years of age, diabetic, and with neuropathic pain.

2. Intervention: Application of physical, topical or oral therapy for the treatment of painful diabetic neuropathy.

3. Comparison: Randomized clinical trials compared with a control group.

4. Outcomes: Measuring of the initial and final pain according to the corresponding scale.

The authors excluded those articles that lacked the pain assessment scale, the demographic characteristics of the sample and the data of the statistical analyses performed that would be necessary for the later realization of the meta-analysis.

3. Data extraction

Surveys were carried out to collect the data of the potentially eligible studies. They gathered the data about the sample size, the type of intervention performed and dosage, the comparison conducted, the results obtained related to the measurement of initial and final pain (with standard deviation), the pain scale used, the duration of the diabetes, the duration of the neuropathic pain, the follow up time of the patients and reference. This extraction was performed by the main author of the present study and an external collaborator. In the absence of indispensable data for the realization of the meta-analysis, the authors of those studies involved were contacted and asked for this information. In all the cases in which the authors were contacted (via e-mail), there was either no reply or

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the e-mail address provided in the article did no longer exist.

4. Measures of quality and risk of bias for the studies

As a quality measure, the Jadad scale was used. This scale described by Jadad et al. (1996) [10] is an instrument that measures the methodological quality of randomized trials in pain research, thus the authors of the present study consider it essential to apply it in the studies selected. The scale was applied to these articles, excluding those that did not obtain a score of 3 or higher.

As a risk of bias assessment, the articles that were not excluded were screened using the tool provided by the Cochrane Collaboration. This tool is based on domains like random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. According to these domains, each study can be classified as high risk, low risk and unclear risk [11,12].

Both the Jadad scale and the Cochrane Collaboration tool for risk of bias assessment were applied in parallel by the main author and an external collaborator. Similar results were obtained from both researchers.

5. Statistical analysis

For the analysis and interpretation of the data of the studies selected, the mean value of the final pain and the effect size of each of the studies were calculated, as measurements of central tendency and dispersion. The standard deviation is the statistical element that takes into account both components, which allows to properly weight each study included in the meta-analysis; therefore, it was considered as inclusion criterion that each study had the mean value and the standard deviation for final pain both in the experimental group and in the placebo group.

The effect size was calculated for each of the articles selected, as well as the global effect size for each of the treatment types. Hedge's g is a standardized measurement of the effect size that allows to compare assessments performed with different tests and scales. This measurement of the effect size does not indicate how many standard deviations the effect has. The interpretation of this measure is based on the g value in absolute value, specifically:
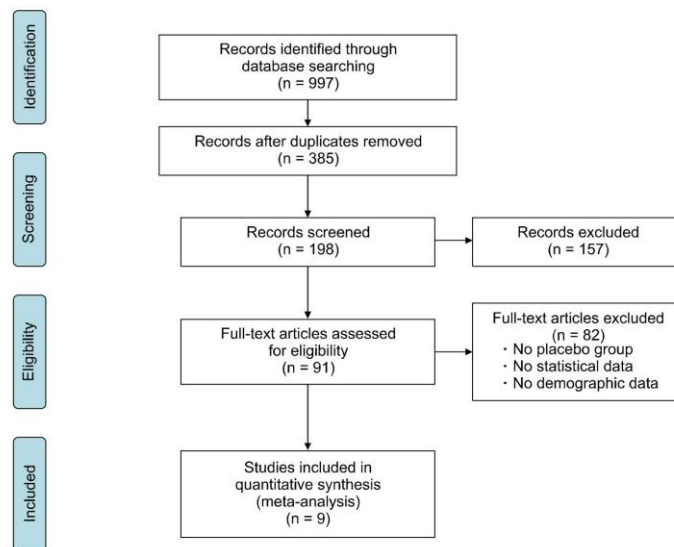

Fig. 1. Flow diagram of the included studies.

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1. absolute g value 0-0.2: no effect
2. absolute g value 0.2-0.5: small effect
3. absolute g value 0.5-0.8: medium effect
4. absolute g value > 0.8: large effect

A forest plot was used for the graphical representation of the confidence intervals of the values of the effect size. It was interpreted in a way that negative values indicate pain improvement. All those confidence intervals that included zero were not considered significant in the improvement of pain.

RESULTS

1. Search results

From the initial search in the different databases, 997 ar-

ticles were obtained for analysis, of which 9 were eventually included after applying the inclusion criteria and analyzing them in detail (Fig. 1).

These 9 articles include topical therapies (clonidine and capsaicin), physical therapies through two types of magnetotherapy, and oral pharmacological therapies such as gabapentin, pregabalin, duloxetine, topiramate and tapentadol. The characteristics of the studies are shown in Table 1 [13-21].

2. Risk of bias and quality measures

Of the articles analyzed using the Cochrane Collaboration tool, "low risk" was obtained in a large percentage of them, with two studies showing this in all their domains. In two other articles there was "high risk" in the domain

Table 1. Characteristics of the Studies Analyzed

Author	Origin	Kind of treatment	Dose or applied therapy	N total	Men	Women	Jadad scale
Goldstein et al., 2005 [13]	USA	Oral medicines (duloxetine)	20 mg/day 60 mg/day 120 mg/day	457	281	176	5
Niesters et al., 2014 [14]	The Netherlands and Denmark	Oral medicines (tapentadol)	500 mg/day	24	14	10	5
Richter et al., 2005 [15]	USA	Oral medicines (pregabalin)	150 mg/day 600 mg/day	246	149	97	5
Campbell et al., 2012 [16]	USA	Topical therapies (clonidine)	3.9 mg/day	179	86	93	5
Rauck et al., 2013 [17]	USA	Oral medicines (gabapentin and pregabalin)	GAB 1200 mg/day GAB 2400 mg/day GAB 3600 mg/day PRE 300 mg/day	420	249	171	5
Weintraub et al., 2009 [18]	USA	Pulsed Electromagnetic Fields	Divided sessions of 10 to 30 minutes (max. 2 hours a day) on the feet for 3 months	194	43.3 % of the PEMF group 44.2% of the sham group	56.7 % of the PEMF group 55.8% of the sham group	5
Weintraub et al., 2003 [19]	USA	Static Magnetic Field	Subjects wear constantly magnetized insoles for 4 month	259	135	124	5
Donofrio et al., 2005 [20]	USA	Oral medicines (topiramate)	600 mg/day	203	106	97	4
Kulkantrakorn et al., 2013 [21]	Thailand	Topical therapies (capsaicin 0.025%)	2 inches of gel topically, 3-4 times a day.	33	16	17	5

GAB: Gabapentin, PRE: Pregabalin, PEMF: Pulsed Electromagnetic Fields.

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"Blinding of participants and personnel" due to the lack of blinding throughout the study, since it does not mention whether or not it was performed (**Fig. 2, 3**).

With respect to the Jadad scale for the measurement of the methodological quality of randomized clinical trials, values over 3 points were obtained in all the articles analyzed, as can be seen in **Table 1**.
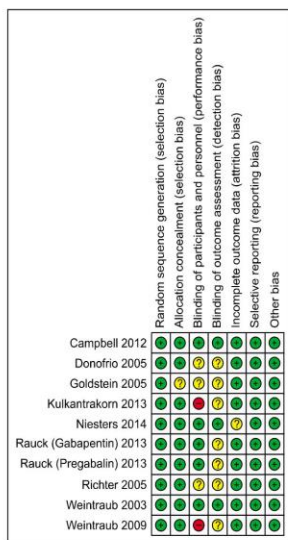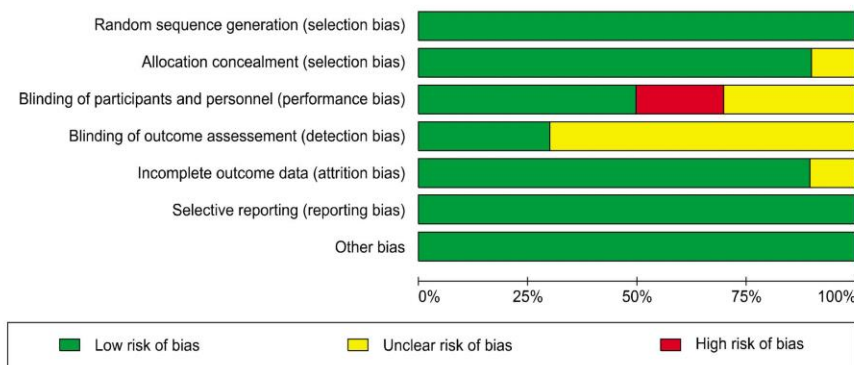

Fig. 2. Risk of bias summary.

3. Meta-analytical results

Regarding the types of therapy included in the meta-analysis, two therapies showed no effect, which were the physical therapy [g: −0.052, 95% CI (−0.229; 0.194)] and the topical therapy [g: −0.238, 95 % CI (−0.524; 0.047)]. The oral therapy obtained a small effect size [g: −0.266, 95% CI (−0.357; −0.175)].

With respect to the individual results of the studies analyzed about the level of final pain, there were two studies with a large effect size, wich are Goldstein et al. [13] about duloxetine at 20 mg/day [g: −1.622, 95% CI (−1.650; −1.594), $P < 0.05$] and Niesters et al. [14] about tapentadol [g: −1.333, 95% CI (−1.594; −1.072), $P < 0.05$]. The study by Richter et al. [15] about pregabalin at 600 mg/day [g: −0.607, 95% CI (−0.980; −0.325), $P < 0.05$] showed a medium effect size. The studies with a small effect size were those by Richter et al. [15] about pregabalin at 150 mg/day (g: −0.407, 95% CI [−0.744; −0.070] $P < 0.05$] and Campbell et al. [16] about clonidine [g: −0.242, 95 % CI (−0.543; −0.058), $P < 0.05$] (**Fig. 4**).

DISCUSSION

The main purpose of this meta-analysis was to determine the level of effectiveness of the treatments included in nine clinical trials analyzed. The results obtained through this study indicate that the clinical trials by Richter et al. [15], Niesters et al. [14], Campbell et al. [16], and Goldstein et al. [13] (in the latter case the dose analyzed was 20

Fig. 3. Risk of bias graph.

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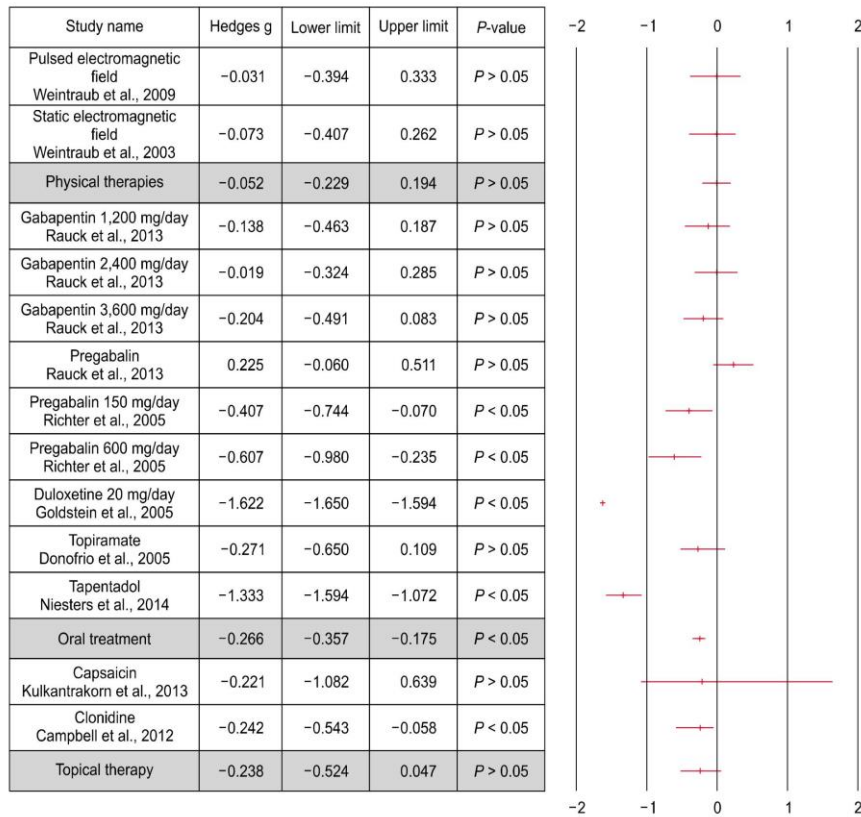| Study name	Hedges g	Lower limit	Upper limit	P-value
Pulsed electromagnetic field Weintraub et al., 2009	−0.031	−0.394	0.333	P > 0.05
Static electromagnetic field Weintraub et al., 2003	−0.073	−0.407	0.262	P > 0.05
Physical therapies	−0.052	−0.229	0.194	P > 0.05
Gabapentin 1,200 mg/day Rauck et al., 2013	−0.138	−0.463	0.187	P > 0.05
Gabapentin 2,400 mg/day Rauck et al., 2013	−0.019	−0.324	0.285	P > 0.05
Gabapentin 3,600 mg/day Rauck et al., 2013	−0.204	−0.491	0.083	P > 0.05
Pregabalin Rauck et al., 2013	0.225	−0.060	0.511	P > 0.05
Pregabalin 150 mg/day Richter et al., 2005	−0.407	−0.744	−0.070	P < 0.05
Pregabalin 600 mg/day Richter et al., 2005	−0.607	−0.980	−0.235	P < 0.05
Duloxetine 20 mg/day Goldstein et al., 2005	−1.622	−1.650	−1.594	P < 0.05
Topiramate Donofrio et al., 2005	−0.271	−0.650	0.109	P > 0.05
Tapentadol Niesters et al., 2014	−1.333	−1.594	−1.072	P < 0.05
Oral treatment	−0.266	−0.357	−0.175	P < 0.05
Capsaicin Kulkantrakorn et al., 2013	−0.221	−1.082	0.639	P > 0.05
Clonidine Campbell et al., 2012	−0.242	−0.543	−0.058	P < 0.05
Topical therapy	−0.238	−0.524	0.047	P > 0.05

Fig. 4. Forest plot of meta-analytic results.

mg/day, since the rest of the doses did not have statistical viability) had a larger effect size regarding the assessment of the final pain of the patients.

These treatments are present in different clinical practice guidelines and recommendations for neuropathic pain, of which the most cited in the literature are those of the American Academy of Neurology (AAN) [7], the National Institute for Health and Care Excellence (NICE) [22], the European Federation of Neurological Societies (EFNS) [4] and the Neuropathic Pain Special Interest Group of International Association for the Study of Pain (NEUPSIG) [23].

The present study shows a high efficiency for the treatments based on gabapentin, duloxetine and pre-

gabalin, which is in line with the aforementioned guidelines, in which they are categorized as first-level drugs for the treatment of painful diabetic neuropathy. In the case of gabapentin, in spite of being a study without effect according to the meta-analysis performed, it can be asserted that the results are positive regarding pain relief in the patients studied, especially at doses of 3600 mg/day.

Two other studies with positive results are those that tackled pain using tapentadol and clonidine. In the case of tapentadol, the results of the present study confirm that it is a useful drug for the treatment of painful diabetic neuropathy; however, the recommendations of the guidelines of the ENS and the NEUPSIG indicate that its use

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is better prescribed for painful processes in acute stages and short periods.

Of the rest of the oral or topical pharmacological therapies, it is worth mentioning that, although they were studies that did not obtain satisfactory results according to the meta-analysis conducted, they did show benefits related to pain relief.

A special case is that of physical therapies, which do not show satisfactory results, and are not valued or described in the recommendation guides, or they are not even recommended by the AAN [7].

The authors found as a limitation the absence of reply from the authors of different articles when contacting them to request more statistical data that would allow them to be included in the meta-analysis.

In conclusion, this meta-analysis indicates the effectiveness of the treatments based on duloxetine, gabapentin and pregabalin. Other drugs, such as tapentadol and topical clonidine, also obtained good results, although the use of the former may be limited to more specific situations. The physical therapies analyzed did not show any type of benefit for diabetic patients with neuropathic pain.

The present study followed a very strict methodology in the analysis and selection of clinical trials. Thereby, despite the fact that it was not possible to include a large number of studies, the results provided can help increase the knowledge about the treatment of painful diabetic neuropathy and the development of clinical practice guidelines for healthcare professionals.

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Anexo 9: Artículos incluidos en el meta-análisis

ORIGINAL ARTICLE

0.025% Capsaicin Gel for the Treatment of Painful Diabetic Neuropathy: A Randomized, Double-Blind, Crossover, Placebo-Controlled Trial

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■ Abstract

Background: Topical therapy may provide additional benefit in patients with painful diabetic neuropathy (PDN). This study was conducted to study the safety and efficacy of 0.025% capsaicin gel in this condition.

Methods: A 20-week, double-blind, crossover, randomized, single-center study enrolled subjects with PDN. They received 0.025% capsaicin gel or placebo for 8 weeks, with a washout period of 4 weeks between the two treatments. Primary efficacy end point was percent change in visual analog scale (0–100 mm) of pain severity. Secondary outcomes were score change in Neuropathic Pain Scale (NPS), short-form McGill Pain Questionnaires (SF-MPQ), proportion of patients who had pain score reductions of 30% and 50%, and adverse event.

Results: Of the 35 subjects screened, 33 were enrolled and 33 completed at least an 8-week treatment period. Intention-to-treat analysis showed no significant improvement in pain with capsaicin gel, compared with placebo with visual analog scale (VAS) score 28.8 mm vs. 34.6 mm ($P = 0.53$). No significant difference between the groups was found in SF-MPQ (7.4 vs. 7.71, $P = 0.95$), NPS (29.4 vs. 31.3, $P = 0.81$), and proportion of patients who had 30% or 50% pain relief. Capsaicin gel was well tolerated with minor skin reaction.

Conclusions: 0.025% capsaicin gel is safe and well tolerated, but does not provide significant pain relief in patients with PDN. ■

Key Words: capsaicin, neuropathic pain, diabetic neuropathy, topical gel

BACKGROUND

Neuropathy is one of the most common complications in both type 1 and type 2 diabetes mellitus. The most common form is a symmetrical, chronic, axonal, length-dependent sensorimotor polyneuropathy.[1] Some patients are asymptomatic, but many patients have sensory symptoms, either negative or positive ones. These symptoms may fluctuate over time. The majority of them also have pain associated with neuropathy, also called painful diabetic neuropathy (PDN).[2] The diagnosis of PDN primarily relies on the patient's description of pain. The symptoms are predominantly symmetrical, distal, and more pronounced at night. Common pain

symptoms are sharp, lancinating, burning, prickling, deep aching, cramping, and gnawing. Upon examination, hyperalgesia and allodynia were frequently found.[3,4] Therefore, it is the most common cause of neuropathic pain.[5] Patients with PDN have a lower quality of life, especially the physical aspect. This condition often persists over time and causes more long-term expenditures.[6,7] Despite recent improvements in chronic neuropathic pain treatment, the pain is often inadequately controlled.

Capsaicin {6-nonenamide, N-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methyl- (6E)} is a natural alkaloid, which is extracted from Solanaceae family plants (red chili peppers). It selectively binds to transient receptor potential vanilloid 1 receptor (TRPV1), a ligand-gated, nonselective cation channel, predominantly expressed on unmyelinated C nerve fibers and causes substance P release. After repeated exposure to topical capsaicin, the local substance P and possibly other neurotransmitters were depleted from sensory nerve endings. This will reduce painful stimuli transmission from peripheral nerves to the central nervous system.[8,9] Defunctionalization of cutaneous nociceptors also plays important role in reducing cutaneous hypersensitivity and pain. It is caused by temporary loss of membrane potential and interruption of neurotrophic factors' transportation. Eventually, phenotypic alteration and reversible retraction of epidermal and dermal nerve fiber terminals occur.[10]

Topical capsaicin formulations are widely used to manage pain. Low-concentration creams, lotions, and patches intended for daily skin application have been available in most countries since the early 1980s. Prescriptions are usually not needed for these self-administered medicines.[10] Previous capsaicin clinical trials in PDN were performed with the concentration of 0.075%, which showed moderate efficacy.[11–13] Burning sensation was the most common cause of the drug discontinuation. Less-concentrated preparations of topical capsaicin may reduce this skin adverse effect. The authors, therefore, studied the 0.025% capsaicin gel preparation for its efficacy and safety in patients with PDN.

METHODS

Trial Design

This was a 20-week, randomized, double-blind, crossover, placebo-controlled trial conducted in an outpatient neurology clinic within a tertiary-care university teaching hospital in a northern suburban area of Bangkok, Thailand.

Patients were assessed at baseline, followed by 8 weeks of treatment with 0.025% capsaicin gel (Capsika-25® gel, Bangkok Drug Company, Bangkok, Thailand) or placebo (vehicle gel) and a 4-week washout period between the two treatments. They were randomly allocated, by computer-generated randomization list in blocks of fours, to 2 groups. The first group received capsaicin gel during the first period and placebo during the second period, while the second group received placebo during the first period and capsaicin during the second period.

The investigators dispensed the drug and performed assessment for efficacy and safety at each visit. In case of adverse event during the study, they were always available to patients by mobile phone. Telephone reminder was used for patients due to visit and for follow-up for missed visits. Demographic characteristics were recorded, and all measured parameters before and after treatment were compared. An independent statistician performed the randomization and assured blinding of procedures.

This study was an investigator-initiated study. It was approved by the Ethical Committee of Faculty of Medicine, Thammasat University and was conducted following the principles of the Declaration of Helsinki and Good Clinical Practice guideline. Written informed consent was obtained from each subject prior to enrolment. This trial was registered with ClinicalTrial.gov (NCT00993070).

Inclusion and Exclusion Criteria

Patients of either sex who had type 2 diabetes for at least 1 year and aged more than 20 years old and who had PDN for at least 1 month were considered for the study. They met all of the following PDN diagnostic criteria: (1) consistent medical history; (2) presence of signs and symptoms of peripheral sensory neuropathy, such as numbness, burning pain, sharp pain, loss of pain, or touch sensation; and (3) a score of more than 4 on the neuropathic pain diagnostic questionnaire (Thai DN4).[14]

The patients were excluded if they had other causes of neuropathy or unstable medical or psychiatric illnesses; were being treated with other investigational drug; had other significant disease or receive medication that may worsen neuropathy during the trial period; underwent invasive intervention for pain relief; or were allergic to

capsaicin.[15] In those who took other pain medications such as anticonvulsants, opioid, local anesthetics, the dosage must have been stable for at least 4 weeks prior to enrolment.

Medication

The study drug was capsicum tincture 45.5 g per 100 g (equivalent to capsaicin 0.025%, Capsika-25® gel) in a plastic tube containing 100 g of gel. Vehicle gel was provided in a matching tube. The drug or placebo was dispensed to patients according to randomized group assignment. The study drug and placebo were provided by Bangkok Drug Company Limited (Bangkok, Thailand).

Patients applied 2 inches of gel topically around the foot and other painful area and rubbed it until dry for 3 to 4 times a day. To avoid unintentional irritation, patients were instructed to wash their hands after applying the gel. Direct questioning and study medication tube accounting were used to assess compliance.

Outcomes

Efficacy. The primary end point of the study was the reduction in the mean pain score from baseline, as assessed by the patient's visual analog scale (VAS) by 0–100 mm. Secondary end points were the assessment of pain by the short-form McGill Pain Questionnaire (SF-MPQ) and Neuropathic Pain Scale (NPS). All measurements were taken at baseline, 2nd, 4th, and 8th week. At the end of each treatment period, a pain intensity score reduction in each individual on the basis of the VAS of 30% and 50% was calculated.[15]

Safety. Safety and tolerability were assessed at each visit. Physical examination, including foot inspection, was performed every visit. Treatment-emergent adverse events (TEAEs) were assessed by clinical and laboratory evaluation as appropriate.

Statistical Methods

Sample Size. The sample size calculation was based on the two by two crossover design[16] with the assumption from the means and SDs observed for VAS pain scores in previous trial of capsaicin in PDN.[12] To detect at least 10% reduction in pain score and 90% power at two-tailed significant level of 0.05, the calculated size sample was 40 patients in each treatment to detect at least 10% pain reduction and standard deviation of 9.5.

Statistical Analysis. Intention-to-treat analysis was used for both the primary and secondary efficacy analyses. It was defined as patients who received at least one dose of study medication and had at least one post-treatment efficacy assessment. Values are expressed as means ± SD, numbers, and percentages. The pain scores, that is, VAS, Neuropathic Pain Scale, and the short-form McGill Pain Questionnaire were compared using the Student's *t*-test. Percentage of patients showing improvement and incidence of adverse events were compared using the chi-square test. A *P* value 0.05 was considered significant, with 2-tailed analysis. STATA program (version 10.0) (College Station, Texas, U.S.A.) was used to perform analysis.

RESULTS

The study was conducted between October 2009 and October 2011.

Patient demographic information, clinical characteristics, and flow through the study period are summarized in Table 1 and Figure 1. Concurrent medications for neuropathic pain among participants included: gabapentin 27.3%, amitriptyline 9.1%, nortriptyline 9.1%, tramadol 6.1%, and pregabalin and paracetamol 3.0%.

Table 1. Baseline Patient Characteristics

Characteristics	Values
Age (years) (min–max)	57.96 (35–76)
Sex: Female	17 (51.5%)
Height (m)	1.64 ± 0.087
Weight (kg)	69.15 ± 13.76
Visual analog scale (mm)	42.7 ± 27.7
Duration of diabetes (years)	11.17 ± 7.46
Duration of pain (years)	4.73 ± 5.13
Thai DN4 score	5.89 ± 1.85
Diabetic complications	
Retinopathy	9 (27.3%)
Nephropathy	6 (18.2%)
Neuropathy	33 (100%)
Comorbidities	
Hypertension	26 (78.8%)
Dyslipidemia	28 (84.8%)
Others	14 (42.2%)
Pain medication	
Tramadol	2 (6.1%)
Amitriptyline	3 (9.1%)
Nortriptyline	3 (9.1%)
Gabapentin	9 (27.3%)
Pregabalin	1 (3.0%)
Paracetamol	1 (3.0%)

Data are means ± SD, or n (%), *n* = 33 patients.
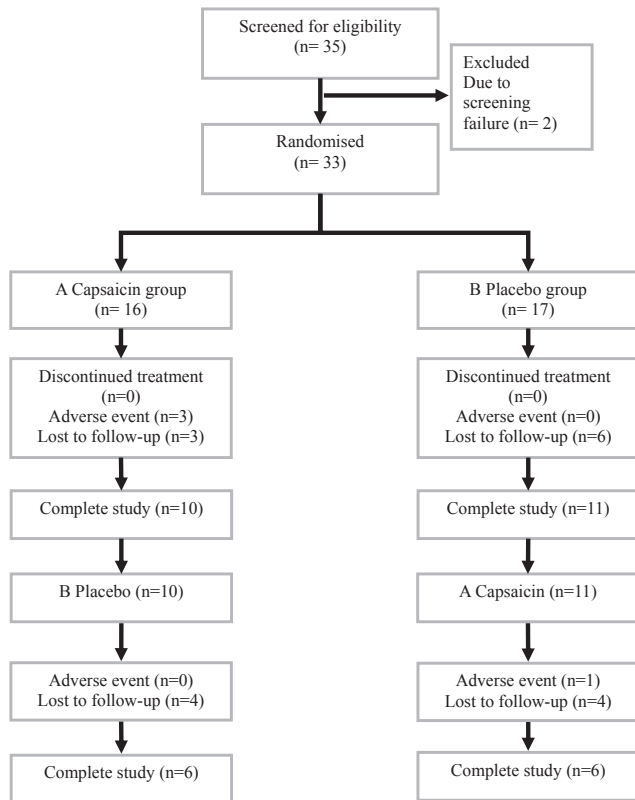VAS, visual analog scale; DN4: neuropathic pain diagnostic questionnaires.

Figure 1. CONSORT statement.

Figure 2. Efficacy of 0.025% capsaicin gel vs. placebo on symptoms of painful diabetic neuropathy (PDN) over 8 weeks of treatment. (A) Visual analog scale (VAS), (B) Neuropathic pain scale (NPS) and (C) Short-form McGill Pain Questionnaires (SF-MPQ).

Of the 35 subjects screened, 33 were enrolled and 33 completed at least an 8-week treatment period. Intention-to-treat (ITT) analysis showed no significant improvement in pain with capsaicin gel, compared with placebo with VAS score of 28.8 mm vs. 34.6 mm ($P = 0.53$; Figure 2A and Table 2). No significant difference between the groups was found in NPS (29.4 vs. 31.3, $P = 0.81$; Figure 2B and Table 2) and SF-MPQ (7.4 vs. 7.7, $P = 0.95$; Figure 2C and Table 2). From VAS data, overall pain relief of 30% was observed in 9/33 (27.3%) and 10/33 (30.3%) of patients with capsaicin and placebo, respectively, and 50% improvement was seen in 6/33 (18.2%) and 9/33 (27.3%) of patients with capsaicin and placebo, respectively. They were not statistically significant ($P = 0.786$ for 30% pain relief and 0.378 for 50% pain relief; Table 3).

The recruitment was prematurely stopped due to unexpected hospital closure for 3 months during the severe flood crisis in Thailand. The reasons for non-compliance included frequent follow-up visits and difficulty in transportation due to long distance from home to th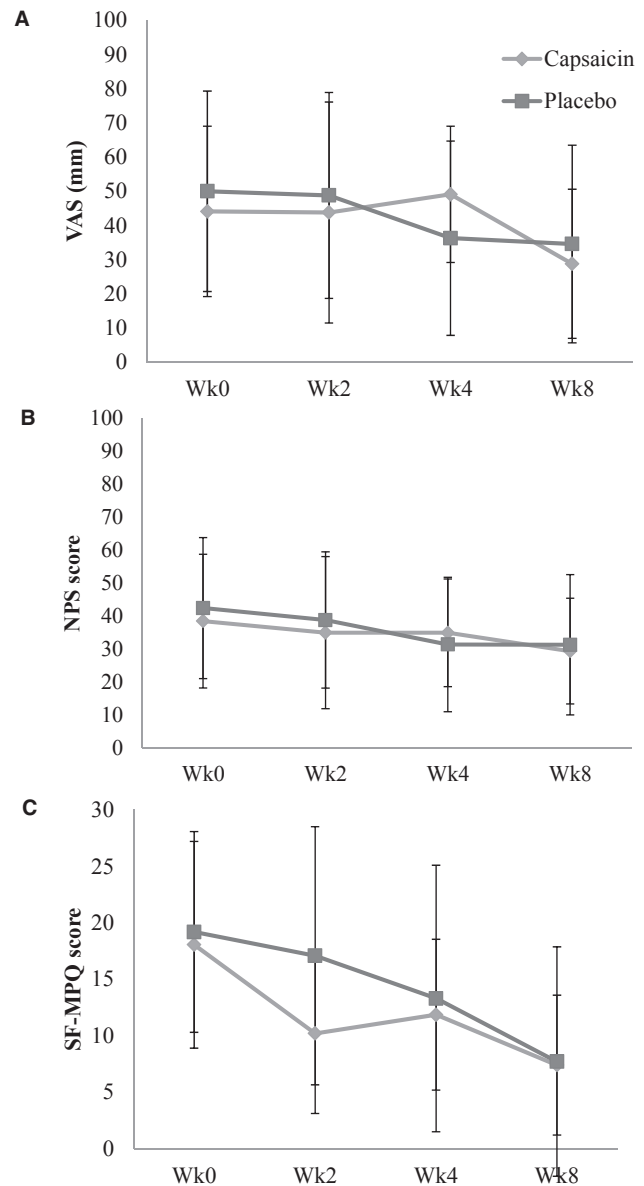e hospital and severe flood during the study period. Baseline scores were similar in the 2 groups; therefore, pooled data were analyzed.

Common TEAEs were local skin reactions (burning, edema, erythema, papules, and pruritus), which were found in 5 (15.2%) patients in capsaicin group vs. no (0.0%) patient in placebo groups. Four patients in the capsaicin vs. no patient in placebo group withdrew because of skin adverse event. Regarding systemic reaction, there was no significant difference in both groups (Table 4).

Table 2. Pain Visual Analog Scale (VAS), Neuropathic Pain Scale (NPS), and Short-Form McGill Pain Questionnaire After Application of 0.025% Capsaicin Gel in Each Visit Over 8 Weeks

Outcome Measurements	0.025% Capsaicin Gel (Mean ± SD)	Placebo (Mean ± SD)	P Value
VAS (mm)			
Wk 0	44.1 ± 2.49	50.0 ± 2.93	0.55
Wk 2	43.8 ± 3.23	48.8 ± 3.01	0.647
Wk 4	4.91 ± 1.92	48.8 ± 3.01	0.155
Wk 8	2.88 ± 2.18	3.46 ± 2.89	0.531
NPS			
Wk 0	38.46 ± 20.76	42.43 ± 21.41	0.630
Wk 2	34.69 ± 23.09	38.79 ± 20.69	0.631
Wk 4	34.92 ± 16.35	31.36 ± 20.43	0.623
Wk 8	29.38 ± 16.07	31.29 ± 21.29	0.805
SF-MPQ			
Wk 0	18.06 ± 9.15	19.18 ± 8.89	0.725
Wk 2	10.20 ± 7.08	17.80 ± 11.42	0.091
Wk 4	11.86 ± 6.67	13.30 ± 11.80	0.775
Wk 8	7.40 ± 6.19	7.71 ± 10.16	0.953

VAS, visual analog scale; NPS, Neuropathic Pain Scale; SF-MPQ, short-form McGill Pain Questionnaire.

Table 3. Proportion of 30% and 50% Pain Relief in Each Group Based on Visual Analog Scale (VAS) Score

Outcomes	Treatment	Number of Patients	Mean VAS (SD)	95% CI	P Value
≥ 30% pain relief	Capsaicin	9	66.57 ± 21.89	49.74–83.39	0.773
	Placebo	10	69.25 ± 17.91	65.44–82.06	
≥ 50% pain relief	Capsaicin	6	77.99 ± 17.23	59.91–96.07	0.559
	Placebo	9	72.79 ± 14.81	61.41–84.17	

Table 4. Treatment-Emergent Adverse Events (TEAEs) Data Are Expressed as *n* (%)

	Capsaicin	Placebo	P Value
Any skin reaction	5 (14.7%)	0 (0.0%)	< 0.01*
Burning sensation	1 (3.0%)	0 (0.0%)	0.50
Edema	1 (3.0%)	0 (0.0%)	0.50
Erythema	1 (3.0%)	0 (0.0%)	0.50
Papules	1 (3.0%)	0 (0.0%)	0.50
Pruritus	1 (3.0%)	0 (0.0%)	0.50
Systemic reaction			
Nausea/vomiting	3 (9.1)	3 (9.1%)	0.69
Hypertension	11 (33.3%)	12 (36.4%)	0.60
Dizziness	1 (3.0%)	0 (0.0%)	0.50
Headache	1 (3.0%)	0 (0.0%)	0.50

*Statistically significant.

DISCUSSION

Topical capsaicin preparation, most studied at 0.075% concentration, has been used in many conditions, such as rheumatoid arthritis, myofascial pain, post herpetic neuralgia, and many skin conditions.[8] A head-to-head comparison trial with amitriptyline in patients with PDN showed comparable efficacy, without systemic side effects.[11] American Academy of Neurology evidence–based guideline recommended 0.075% capsaicin topical preparation as an probably effective treatment option in PDN.[17] In contrast to the European Federation of Neurological Societies recommendation, it did not include capsaicin cream as an effective treatment for PDN due to its limited efficacy and discrepant results.[5] In our study, the results for the primary and secondary end points for pain relief were not achieved for 0.025% capsaicin gel in patients with PDN. However, this concentration was safe and well tolerated. In contrary, the same preparation of lower concentration (0.0125%) provided pain relief greater than vehicle gel with good tolerability in Thai patients with osteoarthritis.[18]

Topical preparations also have certain limitations in variability of pharmaceutical preparation. Several adjuvants were added for viscosity and permeability enhancers, emollient, and preservatives during production. Variation in individual skin condition affects absorption and distribution of the topically applied medication. Moreover, its efficacy also relies on the rate, amount, and depth of skin penetration.[19] Capsaicin is near water insoluble; therefore, the depth of skin penetration is minimal. Higher concentrations may be needed to achieve desirable depth and functional denervation of sensory nerve fibers.

Although a very high concentration at 8% of capsaicin patch was reported to be beneficial in postherpetic neuralgia and HIV-associated neuropathy, it is not suitable for PDN due to its difficult usage and the potential for dangerous side effects. The application of the patch may be impossible on the feet/toes or hands/fingers, which are the affected sites. Theoretically, the application of high concentration of capsaicin may cause more cutaneous denervation, which leads to less protective sensation and possibly increased risk of skin injuries. However, this has not been evident in previous clinical trials for other indications.[10] Episodic application of this patch results in acute localized extensive denervation, which provides pain relief for several months. It is mechanistically different from repeated application of low-concentration capsaicin preparation. A new delivery system, such as nanoparticle preparation, may be more promising. Many new agonists and antagonists of TRPV1 receptor are also currently being evaluated for analgesia, which may have future role in PDN.

Patient's compliance is always an important issue in the treatment of chronic pain, especially in medically ill patients. The frequent application of topical treatment may hinder the compliance. However, this effect in

topical therapy vs. oral drugs has not been adequately studied.[19]

A limitation of this study is the small sample size, high dropout rates, and missing data at some time points. The pooling of results may partially alleviate this issue. Due to the crossover design, many patients who received the placebo during the first phase may have dropped out due to lack of efficacy. Additionally, this trial was interrupted and terminated due to the severe flood in Thailand during study period. At that time, the hospital was closed for several months and land transportation was not possible. Nonetheless, the duration of the evaluable treatment period (8 weeks) in this study was appropriate to evaluate its efficacy. In general neuropathic pain conditions, pain relief was experienced within 6–12 weeks with a single application of 8% capsaicin patch or repeated use of 0.075% capsaicin cream.[10] The frequency of application at 3–4 times a day may also have contributed to noncompliance and dropouts, but it reflected the real-life practice of this topical preparation. However, the dropout rate due to local side effect was low.

In summary, in this crossover study, we found that topical preparation of capsaicin at 0.025% concentration provided no significant benefit in providing pain relief in patients with PDN, but it was safe and well tolerated with minor skin reaction.

ACKNOWLEDGEMENTS

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Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy

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abstract

A length-dependent neuropathy with pain in the feet is a common complication of diabetes (painful diabetic neuropathy). It was hypothesized that pain may arise from sensitized-hyperactive cutaneous nociceptors, and that this abnormal signaling may be reduced by topical administration of the a_2-adrenergic agonist, clonidine, to the painful area. This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. Nociceptor function was measured by determining the painfulness of 0.1% topical capsaicin applied to the pretibial area of each subject for 30 minutes during screening. Subjects were then randomized to receive 0.1% topical clonidine gel (n = 89) or placebo gel (n = 90) applied 3 times a day to their feet for 12 weeks. The difference in foot pain at week 12 in relation to baseline, rated on a 0–10 numerical pain rating scale (NPRS), was compared between groups. Baseline NPRS was imputed for missing data for subjects who terminated the study early. The subjects treated with clonidine showed a trend toward decreased foot pain compared to the placebo-treated group (the primary endpoint; P = 0.07). In subjects who felt any level of pain to capsaicin, clonidine was superior to placebo (P < 0.05). In subjects with a capsaicin pain rating P2 (0–10, NPRS), the mean decrease in foot pain was 2.6 for active compared to 1.4 for placebo (P = 0.01). Topical clonidine gel significantly reduces the level of foot pain in painful diabetic neuropathy subjects with functional (and possibly sensitized) nociceptors in the affected skin as revealed by testing with topical capsaicin. Screening for cutaneous nociceptor function may help distinguish candidates for topical therapy for neuropathic pain.

1. Introduction

A length-dependent neuropathy is one of the most common complications of diabetes. Pain, typically felt in the feet, is a common feature. The analgesic efficacy of oral medications such as pregabalin and duloxetine in painful diabetic neuropathy (PDN) is highly variable, and many patients have difficulty with side effects [25]. It is therefore desirable to find alternative therapies. Prior reports from studies in animals and man have suggested that clonidine may be effective in relieving neuropathic pain when applied topically to the painful area [6,17]. Clonidine is an a_2-adrenergic receptor agonist that was originally approved as an oral product to treat hypertension. Intrathecally applied clonidine was later shown to produce analgesia for both acute and chronic pain [10]. Alpha-2 receptors are also present on nociceptors in the epidermis [26]. Activation of these G-protein-coupled receptors leads to release of an inhibitory G-protein which, in turn, downregulates adenylate cyclase and other second messengers thought to play a role in initiating and maintaining the abnormal excitability of nociceptors [16]. The origin of neuronal signals leading to pain in PDN is unknown, though nociceptors expressed in the skin are a potential target [3]. Given the robust expression of a_2 receptors in cutaneous nociceptors, evidence that nociceptors in the skin may be sensitized in neuropathic pain models, and prior behavioral and clinical data indicating analgesic effects of clonidine, a double-blind randomized study was performed to determine efficacy, tolerability, and safety of topical clonidine to treat PDN. In some

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patients, the skin is profoundly denervated, and in these cases, topical therapy is likely futile. In other patients, the nociceptor innervation of the skin is preserved [11,23,32], and to the extent that abnormal signaling in these nociceptors leads to pain, topical clonidine may have a therapeutic role. Here we provide evidence that the analgesic effect of topical clonidine varies with the painfulness of topical capsaicin applied near the foot. This supports the hypothesis that the efficacy of this topical therapy depends on the presence of nociceptors in the skin, and possibly on the level of sensitization.

2. Materials and methods

2.1. Design

The study was a randomized, double-blind, placebo-controlled, parallel-group study, conducted at multiple centers throughout the United States, that consisted of a screening phase (28 ± 7 days prior to the baseline visit), a baseline phase (7 days prior to treatment plus the baseline visit assessments [day 1]), a 12-week double-blind treatment phase, and a follow-up period (Fig. 1). The protocol and informed consent documents were approved by the appropriate Institutional Review Boards and the trial was registered (ClinicalTrials.gov identifier: NCT00695565). Written informed consent was obtained from each patient before initiation of study procedures.

2.2. Screening of subjects

All subjects were diagnosed to have a length-dependent painful sensory neuropathy affecting the feet attributable to type 1 or type 2 diabetes mellitus based on history, physical examination, and laboratory data. The symptoms followed a stocking-type distribution. Subjects were excluded if they had clinical evidence of other causes of foot pain such as Morton's neuroma, tarsal tunnel syndrome, plantar fasciitis, lumbar radiculopathy, and arthritis. Subjects were also excluded if they had another condition with greater pain intensity, an unstable medical/psychological condition, or an open lesion/skin condition in the area of gel application. The complete list of inclusion and exclusion criteria is provided in Table 1. Physical examination, vital signs, application site assessment, complete medical history, clinical laboratory specimen examination, electrocardiogram (ECG), urine drug screen, and pregnancy test were conducted at screening. Participants also completed questionnaires and underwent sensory testing. Participants discontinued use of ''as needed'' pain medications other than acetaminophen (paracetamol). If they were on other daily pain medications, they were allowed to continue these as long as they agreed to continue stable daily dosing throughout the study.

2.3. Baseline assessment

Subjects recorded the average pain intensity in their feet over the past 24-hour period (average daily pain) using the numerical pain rating scale (NPRS). Eligible subjects (baseline pain rating P4 [average of 7 days prior to treatment]; diaries > 80% complete) underwent baseline measurements that included reassessment of screening procedures and questionnaires, and laboratory assessments (including sampling of plasma levels of clonidine). A subset of participants (97) underwent a 3-mm skin punch biopsy 6 cm above the ankle of either leg in order to quantify intraepidermal nerve fiber density. Epidermal C fibers colocalize with markers of nociceptors and are thought to relate to pain functioning in the skin [26]. This procedure was elective, and sites as well as
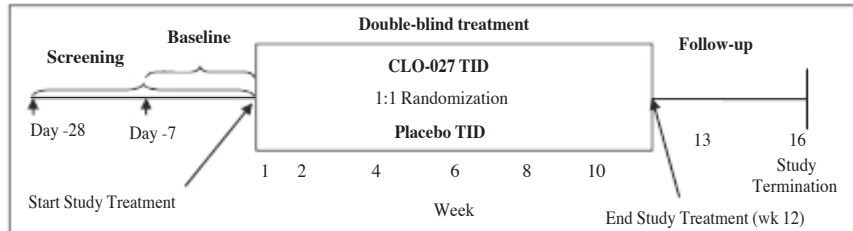

Fig. 1. Timeline. CLO, clonidine; TID, 3 times a day.

Table 1
Inclusion/exclusion criteria.

Inclusion criteria	
1	Between 18 and 80 years of age
2	Established diagnosis of diabetes (type I or II) with pain attributable to a symmetrical stocking distribution neuropathy in the lower extremities
3	Average daily pain score P4 on an 11-point 0–10 numerical pain rating scale (NPRS) in the area of PDN during the baseline phase
4	At least a 6-month history of PDN pain, but 65 years (prior to screening)
5	Stable glycemic control regimen for at least 3 months
6	Stable analgesic regimen for at least 21 days prior to randomization
7	Willing to maintain current medications at their same dose throughout the study
Exclusion criteria	
1	Other chronic pain with greater intensity than their PDN pain
2	Other chronic pain within the region of PDN
3	Any serious or unstable medical or psychological condition
4	Hypotension
5	History of illicit drug or alcohol abuse within a year
6	Cognitive or language difficulties that would impair understanding/completion of the assessment instruments
7	Pregnant or lactating females, planning to become pregnant, or using unreliable means of birth control
8	Received other experimental drugs within 2 months of randomization
9	Prior use of topical clonidine gel
10	Open lesions or skin conditions in the area of gel application
11	Known sensitivity or intolerance to clonidine

PDN, painful diabetic neuropathy.

participants could opt out from participation based on their preference. Labeling was performed with the pan axonal marker PGP 9.5, and density assessment followed validated techniques [35] (Therapath: http://www.therapath.com).

2.4. Questionnaires

The Brief Pain Inventory (BPI) [4] was used to assess pain and functioning. Subjects also underwent tests of sleep (Chronic Pain Sleep Inventory; CPSI) [13] and depression, along with anxiety (Hospital Anxiety and Depression Scale; HADS) [40]. Clinician and Patient Global Impressions of Change (CGIC, PGIC, respectively) were assessed by having the investigator and patient independently rate the overall change in pain status at the final treatment visit [8].

2.5. Psychophysical assessment

During screening, 0.1% capsaicin was applied over a 1-cm diameter area on the pretibial area midway between the calf and ankle of both legs. The pretibial area was selected for placement of the capsaicin stimulus rather than the foot, because the pretibial area is typically also affected by the length-dependent neuropathy, and it was believed that the pain from capsaicin stimulus might otherwise be confused with the ongoing pain in the foot. Notably, the area selected was near the area chosen for skin biopsy used to anatomically quantitate the severity of the small fiber neuropathy (data presented in Results). An occlusive dressing (eg, Tegaderm; 3M, St Paul, MN, USA) was applied over the capsaicin application site, and left in place for 30 minutes. Subjects then rated the capsaicin-induced pain on a 0–10 scale (NPRS) for each leg independently. The responses from the right and left sides were highly correlated ($r^2 = 0.93$, P = 0.001). Therefore, the mean pain rating of the 2 sides was used in further analyses. Vibratory testing was performed on the dorsum of both large toes through use of a 128-Hz tuning fork [20]. Normal, reduced, or absent mechanical sensation was assessed through use of a 10-g (5.07) von Frey monofilament (Center for Specialized Diabetes Foot Services; Mid-Delta Health Systems, Inc, Belzoni, MS, USA) applied to the dorsum of the great toe [20]. An assessment of thermal discrimination was conducted to test the subject's ability to differentiate warmth from cold on the dorsum of each foot using a heated or cooled metal rod.

2.6. Randomization and blinding

Participants were randomized in blocks to receive either 0.1% topical clonidine gel or placebo gel in a 1:1 ratio, double-blinded fashion. Subjects were stratified with regard to baseline pain severity, such that similar numbers of patients with moderate and severe pain were included in the active and placebo groups. The placebo formulation was identical in appearance, consistency, packaging, and labeling. Placebo and active drug were supplied by Arcion Therapeutics (Baltimore, MD, USA).

2.7. Treatment period

Throughout the study, participants recorded their average pain, using the NPRS, over the last 24 hours in a diary each evening before going to bed. Subjects returned to the clinic for visits at weeks 1, 2, 4, 6, 8, 10, and 12 for assessments. Pharmacokinetics and other laboratory tests, physical examination, application site assessments, vital signs, ECG, urine drug screen, urine pregnancy test, HADS, BPI, and CPSI were obtained at clinic visits. Subjects also returned to the clinic approximately 1 week after discontinuation of study medication for a follow-up safety evaluation.

2.8. Drug application

Study medication was self-administered to both feet in the morning, afternoon, and evening. A ''dose'' was defined as the amount of gel delivered with one complete pump (a metered dose) of the mechanical dispensing bottle per foot. Participants were instructed to apply the gel evenly to the toes, between the toes, and top and bottom of the feet extending up to the ankle. The clonidine bottles contained 0.1% clonidine and dispensed 0.65 g of gel (0.65 mg clonidine) per dose. The total daily clonidine dose was 3.9 mg (2 feet, 3 times/day; 0.65 mg Â 6). Prior unpublished studies suggested that .05% is not an effective dose of clonidine, and 0.2% had no greater efficacy than 0.1% clonidine. Safety was assessed by tracking the frequency and severity of adverse events, and comparing pre- and posttreatment urinalysis, blood chemistry, and hematology. Safety was additionally evaluated by assessing local dermal changes and changes in heart rate and blood pressure at study visits.

2.9. Statistical analysis

Analyses of covariance were performed on NPRS change scores (from baseline to 12-week average daily diary ratings; landmark analysis – primary outcome) and (continuous) secondary outcome measures, controlling for baseline scores and treatment-by-study-center interaction. Secondary outcomes of interest included pain (BPI), sleep (CPSI), depression and anxiety (HADS), clinician and patient global impressions of change (CGIC and PGIC), as well as physiological factors. CGIC and PGIC categories were compared between active and placebo groups using a generalized linear model based on maximum likelihood, with specification of the distribution as multinomial. Analyses were also conducted by capsaicin score (a prespecified variable of interest), by separate analyses using the intrapatient capsaicin scores as a dichotomous, independent factor in the analyses of covariance. Missing data for subjects who terminated early were imputed using the baseline scores.

3. Results

Of 464 screened subjects, 182 were randomized (Fig. 2). Of the randomized subjects, one participant from each group was found to be ineligible after randomization (but before dosing) had occurred. In another subject, the baseline NPRS scores were lost after treatment on day 1 and the subject was subsequently lost to follow-up. Of the 179 remaining subjects, 90 received placebo gel and 89 received active gel. Patient demographics, clinical characteristics at baseline, summary questionnaire data, and other variables of interest are presented in Table 2.

The 2 randomized groups were well balanced with regard to demographic characteristics (Table 2). The mean pain level at baseline was 6.5 (n = 179). Nine subjects were diagnosed with type 1 diabetes; one had type 1.5, and all remaining subjects had type 2 diabetes. The mean duration of diabetes was 10 years, with a mean pain duration of 3 years. Use of concomitant neuropathic pain medications was, overall, 44% (39% in the active group and 48% in the placebo group).

3.1. Efficacy

Pain in the intent-to-treat population decreased with time as shown in Fig. 3. At 12 weeks, the decrease in pain in the clonidine group (À2.3; 0–10, NPRS) was greater than the drop in pain in the placebo group (À1.7; D = 0.6, P = 0.07). The responder analysis shown in Fig. 4A and B demonstrates the cumulative proportion of patients who had specified percent decreases in the NPRS at
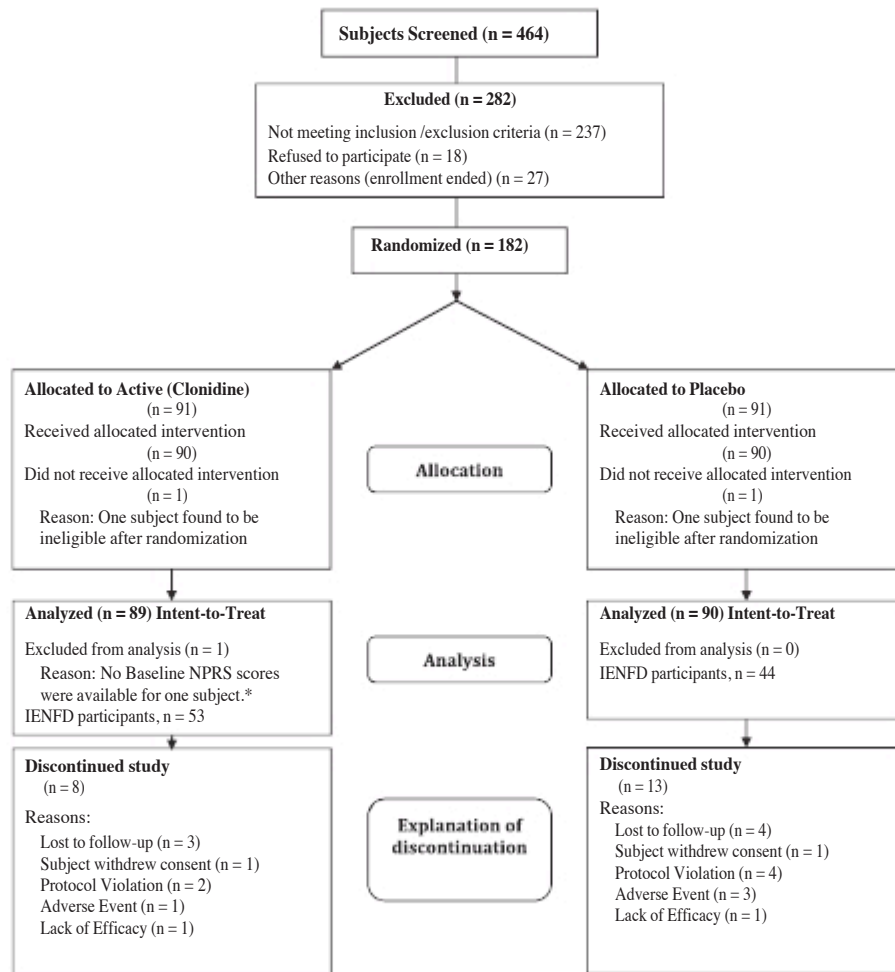
Fig. 2. CONSORT (Consolidated Standards of Reporting Trials) diagram. Immediately after initial dosing, one patient left the study site and removed all pain rating information. The patient could not be reached subsequently. NPRS, numerical pain rating scale; IENFD, intraepidermal nerve fiber density.

12 weeks. For example, in the ITT population, 48% of the clonidine subjects had a 30% drop in pain compared to 40% of the placebo subjects. Changes in the BPI, CPSI, and HADS did not reach statistical significance (Table 2).

To assess nociceptor function, topical 0.1% capsaicin cream was applied under occlusion for 30 minutes in the pretibial area. The capsaicin stimulus evoked pain in 45% of subjects (48% active group; 41% placebo group). The change in pain from baseline in the active vs placebo groups varied with the capsaicin rating as shown in Fig. 3. In the subjects that did not detect capsaicin (rating of 0; n = 99), clonidine had no statistically significant differential effect over placebo at any time point. However, in the subjects who detected any level of pain to capsaicin (capsaicin > 0), clonidine was significantly more effective than placebo (difference in mean = 0.9, 95% confidence interval 0.01–1.76; P < 0.05; Fig. 3). The magnitude of separation between the clonidine- and placebo-treated patients became more pronounced with increasing capsaicin ratings. In subjects with a capsaicin pain rating P2 (0–10, NPRS), the mean decrease in pain was 2.6 (0–10, NPRS) for active, compared to 1.4 for the placebo (difference in mean = 1.2, 95% confidence interval 0.21–2.22; P = 0.01). The responder analysis in Fig. 4b is shown for subjects with capsaicin pain ratings P2.

Male and female subjects did not differ with regard to the response to capsaicin, nor were there any identified ethnic or racial differences. Capsaicin responders also did not significantly differ from nonresponders with respect to duration of diabetes, duration of neuropathic pain, baseline HbA1c, and baseline pain (NPRS – data not shown). The analysis of secondary endpoints demonstrated a similar pattern of efficacy in the capsaicin responders (Table 3). Among capsaicin responders, PGIC and CGIC were statistically significant in favor of clonidine (P = 0.034 and P = 0.018, respectively; Fig. 5), as was change in sleep quality (P = 0.034). A similar analysis was performed based on the results of nonnociceptor sensory function (vibration, assessment of tactile sensibility, and thermal discrimination). No significant correlations emerged between any of these measures and clonidine efficacy or results of capsaicin testing.

Ninety-seven of the 179 subjects underwent a 3-mm skin punch biopsy. Nerve fiber count varied with capsaicin response (Fig. 6). The mean intraepidermal nerve fiber density was 2.7 fibers/mm, SD 3.1 (lower limit of normal is 5.4 fibers/mm [15]). Those who reported any level of pain from the capsaicin (responses > 0) had significantly greater intraepidermal nerve fiber densities (P = 0.042) when compared with subjects rating ''0'' to capsaicin.

3.2. Pharmacokinetics

The typical plasma level of clonidine for treating hypertension is over 1000 pg/mL [29]. In the current examination, the clonidine levels at 2 weeks were similar to those at 12 weeks and generally below the level of detection (10 pg/mL). There were 2 outliers with levels >200 pg/mL (796 pg/mL and 315 pg/mL). The reason for

Table 2
Demographics, clinical characteristics, and outcomes at baseline, and 12 weeks minus baseline.

Variable	Placebo (n = 90) Baseline (BL)	0.1% Clonidine (n = 89) Baseline (BL)	P-value
Age (in years), mean (SD)	57.6 (9.5)	59.4 (9.9)	0.22
Sex, n (%)			
Female	48 (53)	45 (51)	0.77
Male	42 (47)	44 (49)	
Race, n (%)			
Non-Hispanic white	46 (51)	56 (63)	0.19
Hispanic	17 (19)	7 (8)	
African descent	24 (27)	24 (27)	
Other	3 (3)	2 (2)	
Type of diabetes mellitus, n (%)			
Type 1	4 (4)	5 (6)	0.56
Type 1.5	0 (0)	1 (1)	
Type 2	86 (96)	83 (93)	
Duration of diabetes (in years), mean (SD)	9.6 (7.8)	10.7 (8.0)	0.35
Duration of foot pain (in years), mean (SD)	2.9 (1.3)	3.0 (1.3)	0.55
Nerve fiber density (in fibers/mm), mean (SD); (n)	3.2 (3.5); (44)	2.3 (2.6); (53)	0.14
Concomitant medications (%)	48	39	0.25
Capsaicin pain rating, mean (SD) (at Screening; 0–10 NPRS, average of right and left legs)	1.8 (2.7)	1.8 (2.4)	0.97

Variable	Placebo Baseline (BL)	Placebo Change (12 week minus BL)	Clonidine Baseline (BL)	Clonidine Change (12 week minus BL)	P-value
Average pain severity from diary, daily mean (SD, 0–10 NPRS)	6.4 (1.4)	À1.7 (1.9)	6.5 (1.5)	À2.3 (2.2)	0.07*
Experienced >30% reduction in pain, n (%)	36 (40.0)		43 (48.3)		0.34
Experienced >50% reduction in pain, n (%)	26 (28.9)		31 (34.8)		0.49
HbA1c, mean (SD)	7.5 (1.6)	0.1 (0.7)	7.4 (1.6)	0.03 (0.6)	0.47*
BPI – Severity Scale, sum (SD)	25.3 (5.8)	À6.0 (8.2)	25.4 (6.4)	À7.7 (8.9)	0.23*
BPI – Average pain, mean (SD)	6.3 (1.4)	À1.6 (1.9)	6.5 (1.5)	À2.2 (2.2)	0.06*
BPI – Functional Interference Scale, sum (SD)	38.8 (15.1)	À11.8 (14.9)	36.4 (16.9)	À13.5 (17.2)	0.53*
CPSI – Overall sleep quality, mean (SD); (increase = improvement)	37.9 (23.4)	15.9 (32.1)	39.7 (24.7)	18.1 (30.7)	0.40*
HADS – Anxiety Scale, sum (SD)	7.0 (4.1)	À0.5 (2.5)	6.2 (4.1)	À0.7 (3.0)	0.30*
HADS – Depression Scale, sum (SD)	5.9 (4.1)	À0.4 (2.4)	5.0 (3.7)	À0.8 (2.1)	0.11*

NPRS, numerical pain rating scale.

Concomitant medications included anticonvulsants, antidepressants, and opioids; Brief Pain Inventory (BPI; Severity range 0–40, Average pain range 0–10, Functional Interference range 0–70); Chronic Pain Sleep Inventory (CPSI; range 0–100); Hospital Anxiety and Depression Scale (HADS Anxiety range 0–21, Depression range 0–21; <8 is normal, threshold for moderate is 11).

* P-values represent analyses of differences from week 12 to baseline in the active compared to placebo group; no changes were observed at baseline between groups.

these outliers was not apparent, and neither subject had side effects or blood pressure changes consistent with or attributable to excessive clonidine exposure.

3.3. Safety

Adverse events are indicated in Table 4. Skin site reactions were mild and observed only in the placebo group. No significant differences were observed in cardiovascular parameters (blood pressure, heart rate, ECG, serum chemistry, hematology, urine, prothrombin time, partial thromboplastin time, or hemoglobin A1c) and physical examination.

4. Discussion

The results of this study suggest that treatment with topical clonidine reduces pain from diabetic neuropathy and indicates that efficacy depends on the relative level of functionality of nociceptors in the skin. The primary endpoint related to the effects of clonidine in the overall population. Though there was a trend favoring efficacy (P = 0.07), statistical significance was not achieved. The statistical analysis plan stipulated a further analysis relative to the innervation status of nociceptors in the skin as revealed by testing with topical capsaicin.

Studies have shown that the loss of small fiber function and pain sensibility in the skin varies widely among diabetic patients [3,18,33]. The abnormal signals in the nociceptive pathways that lead to pain may, in principal, extend along the neuroaxis (from the skin to the brain). If the skin is severely denervated with regard to nociceptor function, then the target for clonidine, presumed to be the a_2-adrenergic receptor on the epidermal nociceptors, would be lost and clonidine would not have efficacy [2,3,14]. To test for functioning of nociceptors in the skin, topical capsaicin cream 0.1% was applied to the skin above the ankle for 30 minutes at the screening visit. Analgesic efficacy of clonidine over placebo increased with the subjects' response to the capsaicin stimulus. Thus, these data suggest that the analgesic effect of clonidine depends on the presence of functional capsaicin-responsive nociceptors in the skin, and raises the broader issue that neuropathic pain treatments may be guided by results of sensory testing.

The separation between clonidine and placebo was 1.2 on the NPRS scale in subjects with a capsaicin response of P2 (0–10 scale). In the overall population, the separation was 0.6. This separation is within the range seen in other approved therapies. Pregabalin and duloxetine are widely used as oral therapies to treat PDN. Tolle et al. [36] reported benefit of pregabalin of 1.1 over placebo (difference between changes in pain in placebo vs active group) with 600-mg dosing at 12 weeks. With 300-mg dosing, the difference from placebo was only 0.2. In a recent study in Japan [28] (n = 317), the difference over placebo at 300 mg/day was 0.6; at 600 mg/day, the difference was 0.7. For duloxetine at the dose of 60 mg/day, the difference over placebo was about 1.3 at 12 weeks [38], but only 1.0 when the imputation for missing data was the baseline observation carried forward [9].
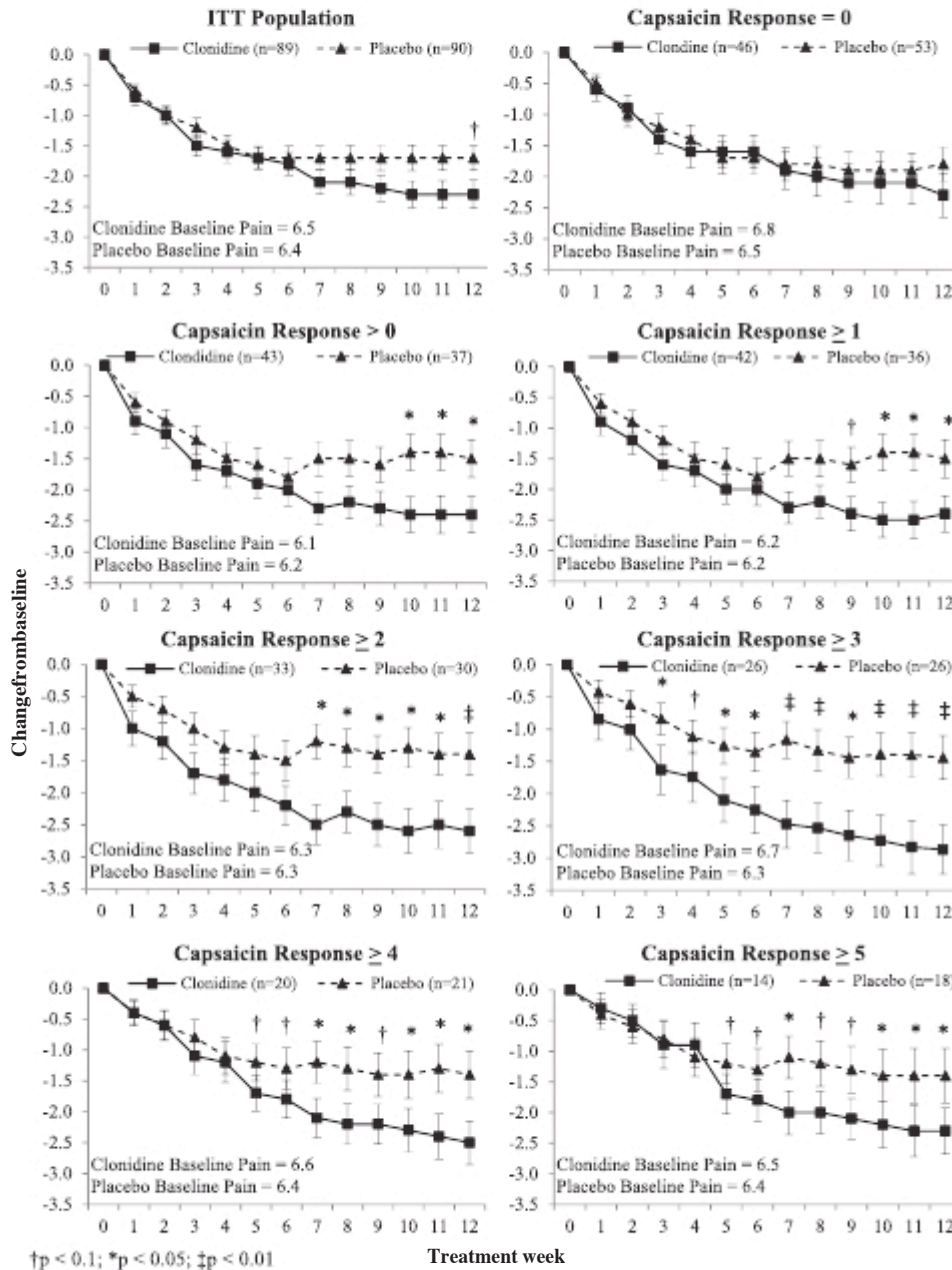
Fig. 3. Mean change in pain by capsaicin response level [(mean ± SEM) Y-axis = DNPRS; X-axis = week]. Effects of Clonidine over Placebo varied with capsaicin response determined during screening. Weekly means of ''average pain over the last 24 hours'' rated on 0–10 numerical pain rating scale. ITT, intent to treat.

4.1. Other sensory and skin biopsy data

Other tests of sensory functions (mechanical, vibration, thermal) did not correlate with the responses to clonidine. These tests were done as simple screens and lacked quantitative rigor. More sophisticated tests of heat and mechanically induced pain have been done in specialized centers [14], but would be difficult to perform in the context of a large multicenter clinical trial. Nevertheless, future studies aimed at assessments of other nociceptor functions and their relation to efficacy of topical treatment will be of value. The capsaicin test reported here was technically simple to apply, took little time, and did not depend on the use of specialized equipment or personnel [34].

To test for anatomical evidence of cutaneous C-fiber pathology, 97 of the 179 subjects underwent a 3-mm skin biopsy. Intraepidermal nerve fibers were labeled with the pan-axonal marker PGP 9.5, and density of fibers was quantified. The C-fiber density in the epidermis, presumed to correspond mainly to the innervation density of nociceptors [1,24,26], was significantly lower in subjects who lacked a response to capsaicin. This anatomical analysis simply assessed the density of epidermal fibers, not the expression of a_2-adrenergic receptors or the presence of sensitization. The capsaicin response, in contrast, is, in a sense, a functional assay, and could suggest sensitization in transient receptor potential V1 channel-positive fibers as well as the anatomical presence of nociceptors.

4.2. Mechanism of action

The blood levels of clonidine in this study were typically below the level of detection (10 pg/mL). Thus, the effects were almost
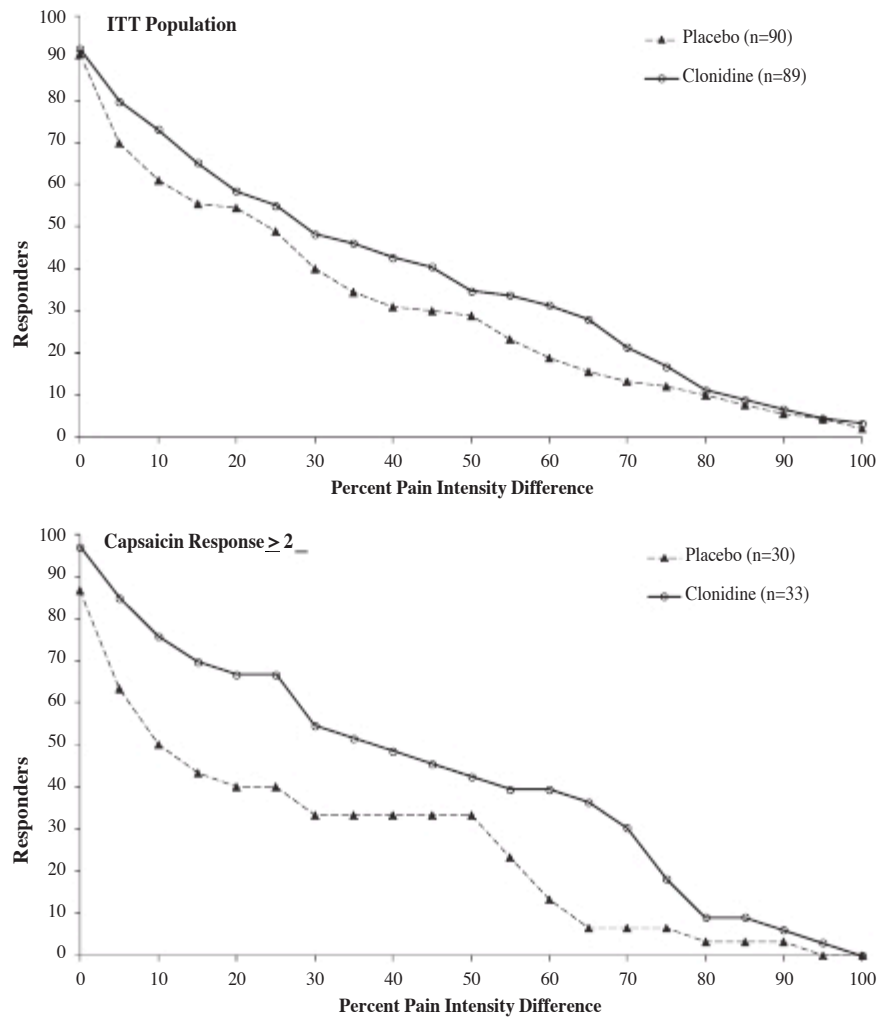
Fig. 4. Cumulative proportion of responder's analysis graph displaying proportion of patients who had a given percentage decrease in pain compared to baseline at week 12 with Clonidine or Placebo. Effects of Clonidine over Placebo varied with capsaicin response determined during screening. Ratings of pain were obtained through 0–10 NPRS. ITT, intent to treat.

Table 3
Demographics and outcomes (change from baseline [12 weeks minus baseline]) for capsaicin responders (capsaicin pain rated P2; 0–10 NPRS).

Variable	Placebo (n = 30)		0.1% Clonidine (n = 33)		P-value
	Baseline (BL)	D from BL to 12-week visit	Baseline (BL)	D from BL to 12-week visit	
Duration of diabetes (in years), mean (SD),	8.8 (5.9)		12.2 (9.3)		0.10
Duration of foot pain (in years), mean (SD)	2.7 (1.3)		2.8 (1.2)		0.57
Nerve fiber density (in fiber/mm), mean (SD); (n)	4.3 (4.2); (18)		2.9 (3.0); (24)		0.20
Capsaicin pain rating, mean (SD) NPRS	5.2 (2.0)		4.5 (2.0)		0.20
Average pain severity from diary, mean (SD) NPRS	6.3 (1.4)	À1.4 (1.8)	6.3 (1.5)	À2.6 (2.0)	0.01[*]
HbA1c, mean (SD)	7.3 (1.5)	0.26 (0.6)	7.4 (1.8)	0.0 (0.6)	0.17[*]
BPI – Severity scale, sum (SD)	25.4 (5.8)	À5.3 (7.8)	25.1 (7.3)	À7.8 (7.2)	0.18[*]
BPI – Average pain, mean (SD)	6.3 (1.5)	À1.3 (1.7)	6.5 (1.6)	À2.2 (1.9)	0.06[*]
BPI – Functional Interference Scale, sum (SD)	37.2 (17.1)	À8.7 (13.2)	37.1 (17.5)	À13.0 (15.2)	0.43[*]
CPSI – Overall sleep quality, mean (SD); (increase = improvement)	37.7 (26.9)	4.4 (32.7)	44.5 (21.5)	13.4 (30.4)	0.03[*]
HADS – Anxiety Scale, sum (SD)	7.8 (4.5)	À0.2 (2.2)	6.4 (4.4)	À0.6 (2.7)	0.30[*]
HADS – Depression Scale, sum (SD)	6.1 (4.5)	À0.8 (2.1)	4.8 (3.5)	À0.4 (1.8)	0.60[*]

NPRS, numerical pain rating scale.

Brief Pain Inventory (BPI; Severity range 0–40, Average pain range 0–10, Functional Interference range 0–70); Chronic Pain Sleep Inventory (CPSI, range 0–100); Hospital Anxiety and Depression Scale (HADS Anxiety range 0–21, Depression range 0–21; <8 is normal, threshold for moderate is 11).

[*] P-values represent analyses of differences from week 12 to baseline in the active compared to placebo group; no changes were observed at baseline between groups.
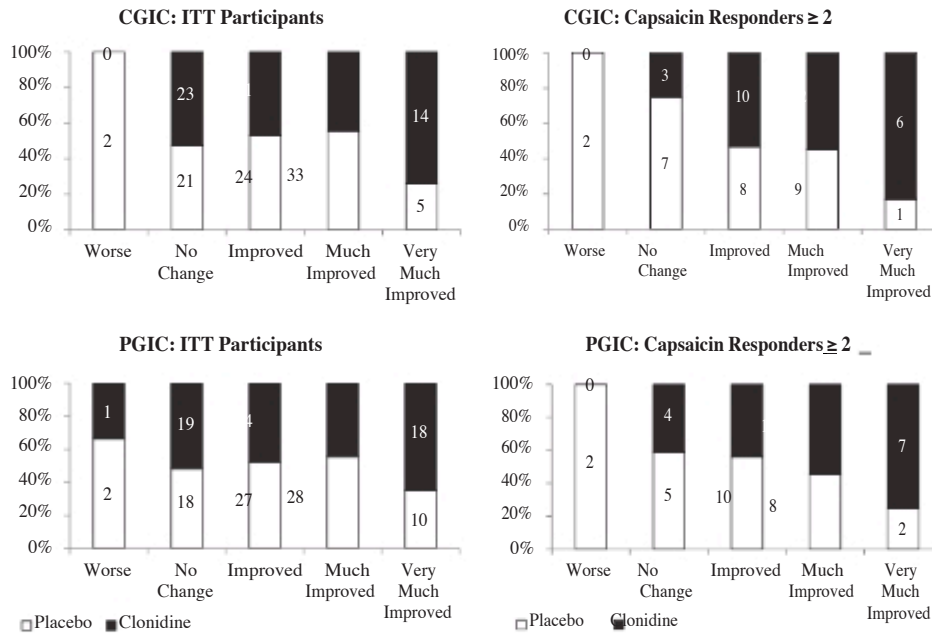
Fig. 5. Clinician and patient global impression of change (CGIC; PGIC) at point of study termination (12 weeks) for capsaicin responders [(P2); Y-axis = percent of patients]. CGIC and PGIC were assessed by having the investigator and patient independently rate overall global impression of change in the subject's pain status at the final treatment visit using a 7-point verbal rating scale. The investigator and subject were asked: ''Relative to Baseline, please rate from among the following choices the subject's total improvement whether or not, in your judgment, it is due entirely to study drug treatment: 'very much improved,' 'much improved,' 'minimally improved,' 'no change,' 'minimally worse,' 'much worse,' or 'very much worse'.'' Percentages are displayed by treatment group on the y-axis, the n for each group is included within each bar. ITT, intent to treat.
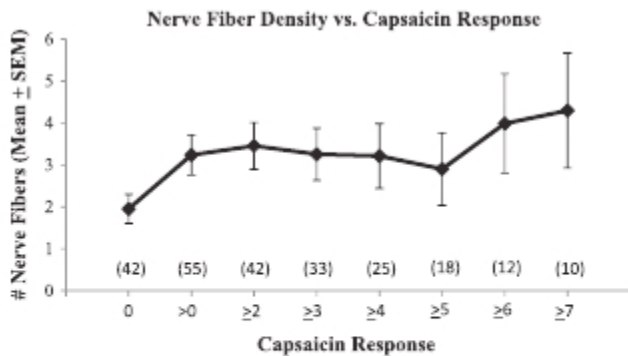

Fig. 6. Nerve fiber count by capsaicin response. Participating subjects (n = 97) received a 3-mm punch skin biopsy on the lower extremity 6 cm above the ankle. Intraepidermal nerve fiber density was determined using the pan-axonal marker PGP 9.5 by a central laboratory (Therapath: http://www.therapath.com). Sites were selected for participation based on willingness to do skin biopsy and a prespecified intent to do the biopsy in about one half of the subjects.

Table 4
Adverse events associated with treatment by group.

System/organ class	Placebo gel (n = 90)	Clonidine gel (n = 89)
Number of patients with P1 related adverse event, n (%)	11 (12.2)	3 (3.4)
General disorders and administration site conditions	2 (2.2)	1 (1.1)
Musculoskeletal and connective tissue disorders	2 (2.2)	0 (0)
Nervous system disorders	2 (2.2)	2 (2.2)
Psychiatric disorders	1 (1.1)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (1.1)
Skin and subcutaneous tissue disorders	5 (5.6)	0 (0)

General disorders, application site irritation/reaction; Musculoskeletal and connective tissue disorders, muscle tightness/pain in extremity; Nervous system disorders, burning sensation/dizziness/headache; Psychiatric disorders, disorientation; Respiratory, thoracic and mediastinal disorders, dyspnea; Skin and subcutaneous tissue disorders, dry skin/eczema/pruritus/rash.

certainly peripherally mediated. Li et al. [17] studied clonidine treatment in a rodent neuropathic pain model and determined that clonidine reversed allodynia and hyperalgesia when applied to the affected paw but not when it was applied to the contralateral side. Application of the clonidine patch relieved hyperalgesia in patients with complex regional pain syndrome, but only in the area of application [5]. Evidence indicates that clonidine is also efficacious in the treatment of PDN when delivered through a transdermal patch applied remotely to the painful area (eg, shoulder or anterior chest region) [39]. In this case, the analgesic mechanism of clonidine may be central as well as peripheral, given that intrathecally administered clonidine has been shown to have analgesic properties [7,21,30].

The discovery that the targeted a_{2A} receptor is expressed directly on nociceptors in the epidermis [27] further supports the hypothesis that clonidine effects are mediated by direct effects in the skin. Clonidine is an agonist for an inhibitory G-protein-coupled receptor [22,31]. Activation of these receptors likely decreases levels of adenylate cyclase and cAMP. Increased levels of these second messengers have been identified as a source of increased excitability of nociceptors and as a mechanism of neuropathic pain. Adenylate cyclase upregulation may also lead to phosphorylation of the transient receptor potential V1 channel and therefore, sensitize nociceptors to capsaicin stimulation. This observation provides further impetus to use capsaicin testing as a tool to identify candidates for clonidine treatment [12,19,37].

4.3. Conclusions

Topical clonidine gel significantly reduced the level of pain in subjects with diabetic neuropathy in whom there are functional (and possibly sensitized) nociceptors in the affected skin. This

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study provides support for the view that quantitative sensory testing may aid in identification of the appropriate treatment for a given patient. The treatment with clonidine was safe and without the problematic side effects typically associated with systemic therapies. Further research is warranted to corroborate the efficacy and safety of topical clonidine as a treatment of PDN and, possibly, other neuropathic pain states. Drugs with effects in preclinical trials targeting specific mechanisms have often failed in phase-2 and -3 efficacy trials. This could be due in part to the heterogeneity of mechanisms in the patients. In future drug trials, it may prove useful to screen for nociceptor function in the skin as a way to optimize identification of effective topical therapies.

Conflicts of interest statement

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Duloxetine vs. placebo in patients with painful diabetic neuropathy[*]

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Abstract

The aim of this study was to examine the efficacy and safety of duloxetine, a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine, in the management of diabetic peripheral neuropathic pain. Serotonin and norepinephrine are thought to inhibit pain via descending pain pathways. In a 12-week, multicenter, double-blind study, 457 patients experiencing pain due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus were randomly assigned to treatment with duloxetine 20 mg/d (20 mg QD), 60 mg/d (60 mg QD), 120 mg/d (60 mg BID), or placebo. The diagnosis was confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument. The primary efficacy measure was the weekly mean score of the 24-h Average Pain Score, which was rated on an 11-point (0–10) Likert scale (no pain to worst possible pain) and computed from diary scores between two site visits. Duloxetine 60 and 120 mg/d demonstrated statistically significant greater improvement compared with placebo on the 24-h Average Pain Score, beginning 1 week after randomization and continuing through the 12-week trial. Duloxetine also separated from placebo on nearly all the secondary measures including health-related outcome measures. Significantly more patients in all three active-treatment groups achieved a 50% reduction in the 24-h Average Pain Score compared with placebo. Duloxetine treatment was considered to be safe and well tolerated with less than 20 percent discontinuation due to adverse events. Duloxetine at 60 and 120 mg/d was safe and effective in the management of diabetic peripheral neuropathic pain.
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Keywords: Duloxetine; Cymbalta[w]; Diabetic neuropathy; Antidepressant; Pain; Efficacy; Safety/tolerability

1. Introduction

Diabetes is commonly associated with a peripheral neuropathy that often results in significant pain. The pain has been described as an 'aching, burning, stabbing, or tingling' sensation, and often affects sleep. Tricyclic antidepressants (TCAs), certain anticonvulsants (e.g. gabapentin), and opioid analgesics are currently used to treat the neuropathic pain due to diabetic peripheral neuropathy, but often are limited by efficacy or significant side effects (Kapur et al., 1992; McQuay et al., 1996).

Serotonin (5-HT) and norepinephrine (NE) have been implicated in the modulation of endogenous analgesic mechanisms via the descending inhibitory pain pathways in the brain and spinal cord (Basbaum and Fields, 1984; Clark and Proudfit, 1993; Fields and Basbaum, 1999; Fields et al., 1991). An imbalance in these inhibitory mechanisms may contribute to central sensitization and hyperexcitability of the spinal and supraspinal pain transmitting pathways leading to persistent pain [reviewed by Coderre and Katz (1997)] (Ren and Dubner, 2002).

Duloxetine hydrochloride [(Cymbalta[w]), (C)-N-methyl-g-(1-naphthalenyloxy)-3-(2-thiopene)-propanamine] is a relatively balanced and potent dual reuptake inhibitor of both 5-HT and NE (SNRI) transporters with weak affinity for the dopamine transporter and insignificant affinity at more than 60 neurotransmitter receptors including muscarinic, histamine, opioid, glutamate and GABA receptors

and sodium, potassium, and calcium channel sites (Wong and Bymaster, 2002).

Duloxetine is effective in animal models of persistent and neuropathic pain (Iyengar et al., 2004) suggesting that duloxetine could be efficacious in the treatment of persistent pain conditions in humans. Since efficacy occurs at doses that do not impair performance on the rotorod test of neurological function, duloxetine is likely to be non-sedating and non-ataxic (Iyengar et al., 2004), making it a good clinical candidate.

In several randomized, double-blind, placebo-controlled studies, duloxetine at 60–120 mg per day (Detke et al., 2002a,b; Goldstein et al., 2002; Nemeroff et al., 2002) was an effective treatment for major depressive disorder (MDD) based on traditional measures of efficacy, such as the Hamilton Depression Rating Scale. Duloxetine also produced significant improvement on visual analog scales (VAS) ratings of painful physical symptoms associated with depression, including overall pain, back pain, shoulder pain, headache, and general somatic symptoms, despite the fact that patients were not selected for pain type or pain severity and the studies were not statistically powered for these measures. Path analysis demonstrated that greater than 50% of the reduction in painful physical symptoms of MDD was a direct effect of duloxetine, rather than a secondary effect of improving depression.

Consistent with duloxetine's effects on the painful physical symptoms in MDD and the existing evidence that dual 5-HT and NE reuptake inhibitors are effective in treating pure pain disorders such as neuropathic pain conditions (Sindrup and Jensen, 1999), the potential analgesic efficacy of duloxetine was evaluated in patients with neuropathic pain due to diabetic peripheral neuropathy who did not have depression. The current study describes the efficacy and safety of duloxetine in reducing pain severity in diabetic peripheral neuropathic pain (DPNP) patients.

2. Methods

2.1. Study design

This was a parallel-group, double-blind, randomized, placebo-controlled study of patients who met criteria for diabetic neuropathy as assessed by history and the physical exam portion of the Michigan Neuropathy Screening Instrument (MNSI) (Sheehan et al., 1998). The primary objective was to evaluate the efficacy of duloxetine 20, 60, or 120 mg/d (administered 20 mg QD, 60 mg QD and 60 mg BID, respectively), on the treatment of pain associated with diabetic neuropathy as compared with placebo. Each site's ethics committee approved the study protocol in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent prior to participation in any study-related procedures.

2.2. Patients

Patients, at least 18 years of age, had daily pain due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus, which was present for a minimum of 6 months. This pain had to have begun in the feet with relatively symmetrical onset. The diagnosis was confirmed by a score of at least 3 on the MNSI. Patients were required to have a minimum score of 4 on the 24-h Average Pain Score rated on an 11-point (0–10) Likert scale. Patients were excluded if, over the past year, they met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Axis I diagnosis of MDD, depression-partial remission, dysthymic disorder, generalized anxiety disorder, alcohol or eating disorders as determined by the Mini International Neuropsychiatric Interview (MINI). Patients were excluded if they had any current or historical DSM-IV diagnosis of mania, bipolar disorder, or psychosis as determined by the MINI. Patients were also excluded if they had pain that could not be clearly differentiated from, or conditions that might interfere with, the assessment of the DPNP, such as peripheral vascular disease (ischemic pain); neurological disorders unrelated to diabetic neuropathy (e.g. phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation (e.g. plantar ulcer); other painful conditions (e.g. arthritis). Patients were also excluded if they had a history of substance abuse or dependence within the past year or had a positive urine drug screen, if they received treatment within the last 30 days that had not received regulatory approval, had taken excluded medications within 7 days of baseline, received treatment with a MAOI or fluoxetine within 30 days of baseline, or had used an opioid within 3 days of baseline. Patients were allowed to take a maximum of 4 g of acetaminophen per day, but no other analgesic medication used to treat diabetic neuropathic pain.

2.3. Treatments

Patients (457) were randomly assigned to duloxetine 20, 60, 120 mg/d, or placebo in a 1:1:1:1 ratio for the 12-week therapy phase (see Fig. 1) as determined by a computer-generated random sequence using an interactive voice response system (IVRS). Patient numbers were assigned consecutively at each study site to each patient who entered the study. The IVRS was used to assign blister cards containing study drug to each patient confirmed through IVRS entry of a confirmation number found on the card. Patients were seen weekly for the first 5 weeks of treatment and then bi-weekly thereafter.

2.4. Efficacy measures

Efficacy was assessed primarily using the weekly mean change from baseline to endpoint on the 24-h Average Pain Score [11-point (0–10) Likert scale] (referred to as the 24-h Average Pain Score, hereafter), computed from diary scores recorded at the time of the evening dose between two site visits. In addition to average pain severity, the diary included ratings of worst pain severity over the prior 24 h, average pain during the night once they had gone to bed, and acetaminophen use over the past 24 h. Secondary measures included Average Daily Severity and Average Night Pain Severity (weekly mean scores of the 24-h Average Pain Severity and Average Night Pain Severity), Worst Pain Severity,
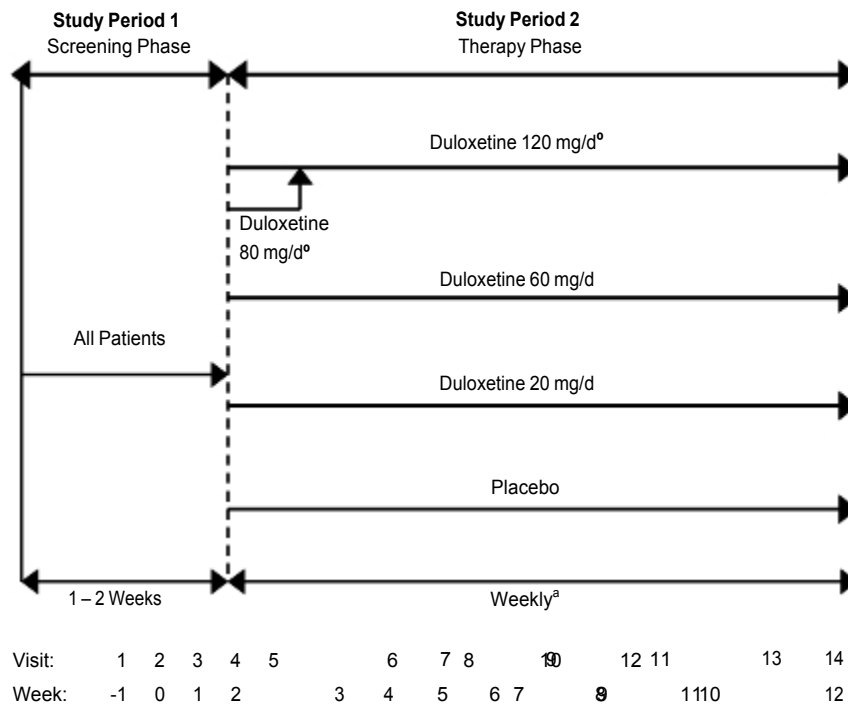
a Visits 7, 9, 11, 13, and 15 were phone visits only.
o Bi-daily dosing administration.

Fig. 1. Illustration of study design.

severity and interference portions of the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994) at each visit; Clinical Global Impression of Severity (CGI-Severity) Scale (NIMH 1976) and Patients Global Impression of Improvement (PGI-Improvement) Scale (Guy, 1976) at randomization, Weeks 4, 8, and 12; the sensory portion of the Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987), Dynamic Allodynia at randomization and Week 12, the Short Form-36 Health Status Survey (Ware et al., 1993), and the EQ-5D version of the Euro Quality of Life instrument (Kind, 1996). Changes in mood and anxiety were measured using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and the Beck Anxiety Inventory (BAI) (Beck et al., 1988), respectively, at randomization and Week 12.

2.5. Safety assessments

Safety measures recorded at every visit included spontaneously reported adverse events, concomitant medications, weight, supine heart rate and blood pressure, and the occurrence of significant hypoglycemic events. Blood chemistry, hematology, HgbA1c, and lipids were collected at Visit 1 and Week 12. For those who discontinued from the study, those assessments were collected at their last visit.

Sustained hypertension was defined as three consecutive visits with the following:

† Sitting systolic blood pressure R130 mmHg and an increase from baseline of 10 mmHg, or
† Sitting diastolic blood pressure R85 mmHg and an increase from baseline of 10 mmHg.

2.6. Statistical analysis

This study was designed to enroll 440 patients. With 110 patients per arm, this study would have at least 90% power to detect a treatment group difference of K1.20 points in the weekly mean of 24-h Average Pain Severity between duloxetine 60 mg BID and placebo treatment groups after 3 months of acute therapy. The sample size was determined using a 2-sided test with aZ0.05 and assuming a common standard deviation of 2.2 and a discontinuation rate of 35%.

All analyses were conducted on an intent-to-treat basis. All randomized patients were included in safety analyses and all randomized patients with at least one post-baseline assessment were included in the efficacy evaluations. After randomization, weekly average scores on 24-h average pain, worst pain, and night pain were calculated for the diary entries collected in days between weeks; the baseline for the three variables was calculated by taking the average of last three non-missing diary data given the consideration that previous medications had effect on the first few days after the screening visit. For either case, the mean score was set to be missing if the number of diary entries was less than 3.

A likelihood-based mixed-effects model repeated measures analysis was the protocol-specified primary efficacy analysis for continuous efficacy measures with longitudinal observations. The model included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors. The primary treatment comparisons were the contrasts between duloxetine treatment groups and placebo at
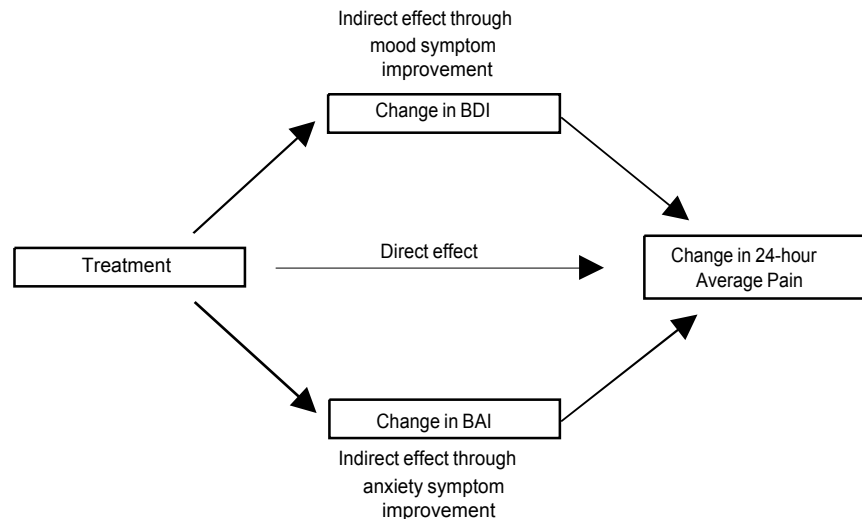
Fig. 2. Causal relationship in the path analysis on 24-h average pain.

the last visit of the study (Week 12) on the change scores. Satterthwaite's approximation was used to estimate denominator degrees of freedom. The dose–response trend for the primary efficacy measure was tested using a repeated measures analysis model where therapy was replaced by dosage and placebo was excluded and the overall dose effect was reported. For the continuous efficacy measures collected once at baseline and once at the last visit of the study, change from baseline to endpoint was assessed using an ANCOVA model, which contained terms of treatment, investigator, and baseline. For either statistical model, Type III sum-of-squares for the least-squares mean was used for testing the differences between treatment groups.

Path analysis (Retherford and Choe, 1993) was performed to test the direct treatment effect on pain reduction. In this analysis, pre-specified pathways (Fig. 2) described the causal relationships for the testing: the treatment has effect on pain reduction (direct effect), and the treatment effect on mood or anxiety symptoms has impact on pain reduction (indirect). The significance of the direct treatment effect was tested by a Student's t-test in the regression model where change in 24-h average pain was a dependent variable, and treatment, baseline, investigator, change on BDI, and change on BAI were regressors. In addition, with two other regression models on change on BDI and BAI, respectively, the indirect treatment effect via change in BDI (or BAI) was a result of multiplying treatment coefficient by the coefficients of the corresponding change in the first described regression model. The percentage of direct and indirect effects on the total treatment effect was computed and presented. When an indirect pathway had no impact on pain reduction (i.e. the coefficient between pain reduction and change was positive) that particular path was removed from the path analysis.

Continuous baseline measures and continuous safety measures were evaluated using a fixed effect (treatment, investigator) ANOVA. Categorical variables were analyzed using Fisher's exact test. Average daily dose of acetaminophen use was calculated over days on therapy for each patient. Treatment group differences were evaluated using the ANOVA model on the rank-transformed data since the distribution of the data was skewed. For the same

reason, the rank transformed change from baseline to endpoint, the last non-missing observations during the trial, on laboratory analytes were analyzed using the ANOVA model.

For all the analyses, treatment effects were tested at a 2-sided significance level of 0.05. Throughout this manuscript, the term 'significant' indicates statistical significance ($P \% 0.05$), and the term 'mean change' refers to the least-squares mean change for the continuous efficacy variables.

3. Results

3.1. Patient disposition

Patient disposition is shown in Fig. 3. Of the 763 screened patients, 457 patients entered and 344 (75.3%) completed the study. The duloxetine 60 mg/d (13.2%) and 120 mg/d (19.5%) treatment groups had more discontinuations due to adverse events than the placebo treatment group (5.2%; $P ! 0.001$).

3.2. Demographics

The patient demographics and baseline assessments are shown by treatment group in Table 1. Most patients had Type 2 diabetes mellitus (88.4%) with a mean duration of diabetes of 11.3 years and of diabetic neuropathy for 3.7 years. The majority of patients were male with percentages ranging from 51% in the placebo group to 69% in the 60 mg/d treatment group.

3.3. Efficacy

Mean change from baseline to each post-baseline visit on the 24-h Average Pain Score, shown in Fig. 4, and the mean change from baseline to endpoint during the 12-week study,
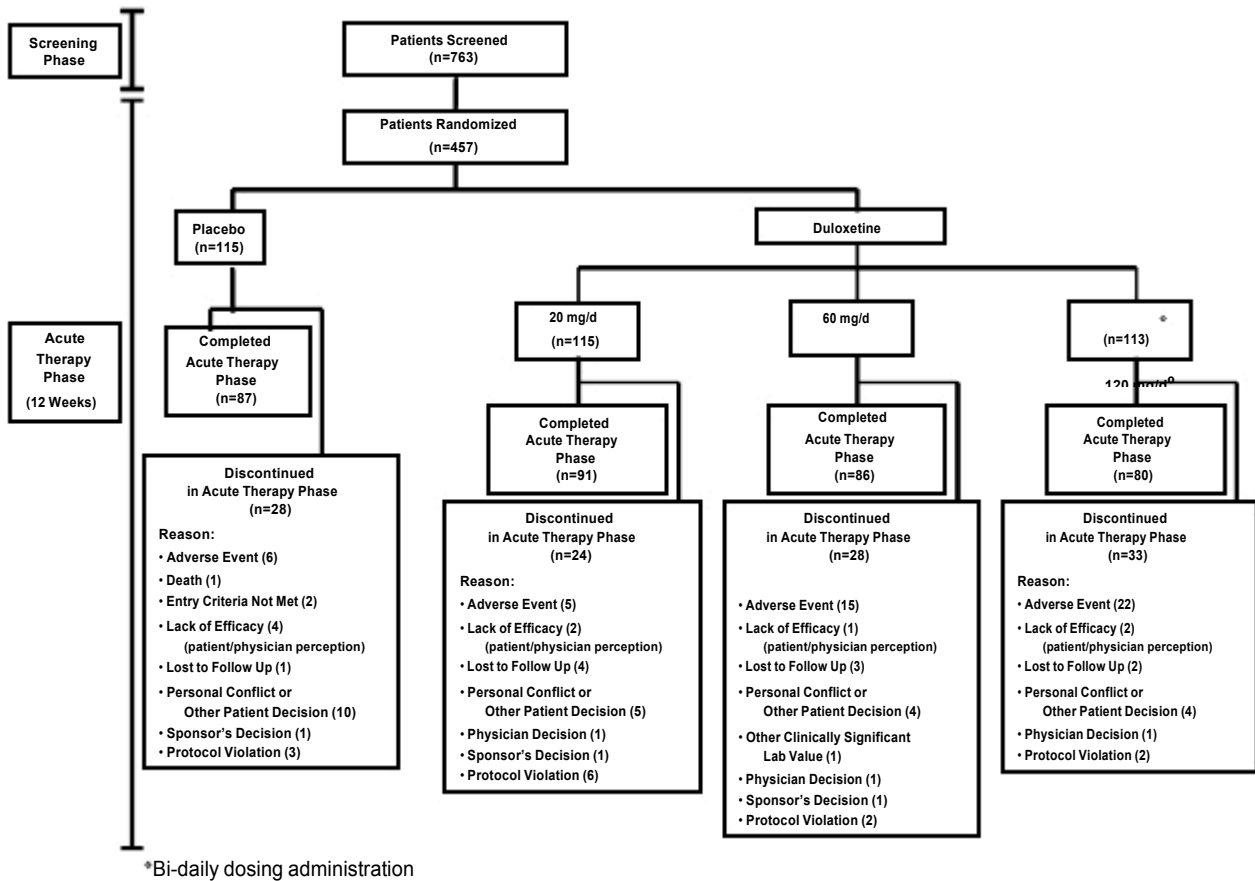
Fig. 3. Patient disposition.

Table 1
Demographics and baseline assessments

Variable	Placebo (n꞊115)	Duloxetine			Total	P-value
		20 mg/d (n꞊115)	60 mg/d (n꞊114)	120 mg/d[a] (n꞊113)	(N꞊457)	
Age, years (SD)	60.4 (10.5)	60.3 (10.9)	59.2 (11.6)	60.5 (10.8)	60.1 (10.9)	0.786
Gender						
Female, n (%)	56 (48.7)	40 (34.8)	35 (30.7)	45 (39.8)	176 (38.5)	0.033
Male, n (%)	59 (51.3)	75 (65.2)	79 (69.3)	68 (60.2)	281 (61.5)	
Race (origin)						
Caucasian, n (%)	89 (77.4)	85 (73.9)	88 (77.2)	91 (80.5)	353 (77.2)	
African, n (%)	11 (9.6)	12 (10.4)	8 (7.0)	6 (5.3)	37 (8.1)	
Hispanic, n (%)	12 (10.4)	12 (10.4)	13 (11.4)	14 (12.4)	51 (11.2)	0.915
Other, n (%)	3 (2.6)	6 (5.3)	5 (4.4)	2 (1.8)	16 (3.5)	
Height (cm)	170 (11)	172 (11)	174 (10)	171 (11)	172 (11)	0.046
Weight (kg)	94 (22)	93 (19)	99 (24)	96 (21)	96 (21)	0.128
Type of diabetes mellitus						
Type I, n (%)	11 (9.6)	17 (14.8)	14 (12.3)	11 (9.7)	53 (11.6)	0.565
Type II, n (%)	104 (90.4)	98 (85.2)	100 (87.7)	102 (90.3)	404 (88.4)	
Duration of diabetes (years)	11.4 (11.3)	12.1 (9.5)	11.4 (8.2)	10.1 (9.0)	11.3 (9.6)	0.438
Duration of diabetic neuropathy (years)	4.0 (4.1)	3.7 (3.7)	3.8 (4.4)	3.5 (2.8)	3.7 (3.8)	0.695
MNSI	5.1 (1.6)	5.4 (1.6)	5.1 (1.6)	5.3 (1.5)	5.2 (1.6)	0.555
Average 24-h pain severity	5.8 (1.5)	5.9 (1.6)	6.0 (1.7)	5.9 (1.4)	5.9 (1.6)	0.627
CGI-Severity	4.4 (0.9)	4.4 (0.9)	4.3 (1.0)	4.4 (0.9)	4.4 (0.9)	0.450
BDI-II total	7.3 (7.8)	8.1 (6.8)	7.1 (6.4)	6.7 (5.5)	7.3 (6.7)	0.463
BAI total	8.4 (7.5)	9.2 (7.4)	7.8 (6.1)	8.8 (8.6)	8.6 (7.4)	0.556

MNSI, Michigan Neuropathy Screening Instrument; CGI-Severity, Clinical Global Impressions of Severity; BDI-II total, Beck Depression Inventory II total;
BAI total, Beck Anxiety Inventory Total; SD, standard deviation.
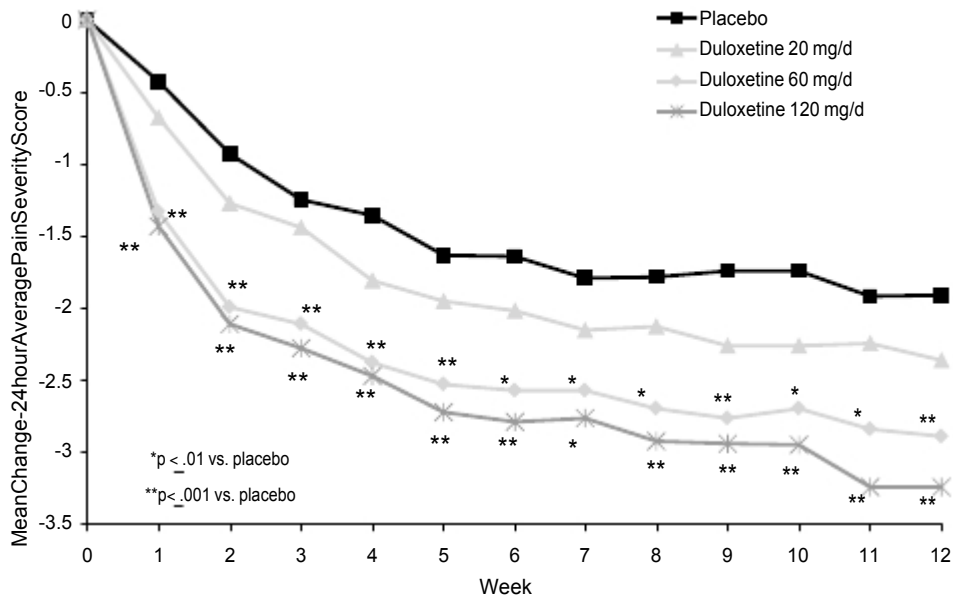[a] Bi-daily dosing administration.

Fig. 4. Mean change from baseline in 24-h average pain severity for all randomized patients over 12 weeks of double-blind therapy.

presented in Table 2, demonstrate dose-related efficacy (PẐ0.005 for testing of linear trend). Duloxetine 20 mg/d demonstrated a non-significant decrease in pain severity compared with placebo. The duloxetine 60 and 120 mg/d treatments significantly reduced pain severity beginning at Week 1 and continuing throughout the study compared with placebo, while there was no significant difference between

the duloxetine 60 and 120 mg/d groups. The mean difference between 60 mg/d and placebo at endpoint was K1.17 (95% CI: K1.84 to K0.50) and that between duloxetine 120 mg/d and placebo was K1.45 (95% CI: K2.13 to K0.78). A 50% reduction in the 24-h Average Pain Score was achieved by 29 (26%) in the placebo group, 46 (41%) in the duloxetine 20 mg/d group, 55 (49%) in

Table 2
Mean change in efficacy and health outcome measures

	Placebo		Duloxetine					
			20 mg/d		60 mg/d		120 mg/d	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
24-h average pain score [a]	88	K1.91 (0.22)	91	K2.36 (0.21)	88	K2.89 (0.22)	80	K3.24 (0.23)
24-h worst pain score[a]	111	K2.09 (0.24)	111	K2.78 (0.23)	112	K3.31 (0.24)*	109	K3.72 (0.24)***
Night pain score[a]	111	K2.20 (0.23)	111	K2.48 (0.22)	112	K2.91 (0.23)*	109	K3.45 (0.24)***
BPI average pain severity[a]	112	K2.04 (0.21)	110	K2.25 (0.21)	113	K2.81 (0.21)**	109	K3.07 (0.22)***
BPI interference - general activity[a]	89	K1.72 (0.21)	91	K1.87 (0.21)	88	K2.43 (0.21)*	81	K2.54 (0.22)**
BPI interference[a] (Avg. of 7 inter-ference questions)	112	K1.73 (0.17) 110	K1.73 (0.17) 113	K2.33 (0.17)**	109	K2.30 (0.18)*		
CGI-Severity[a]	111	K0.83 (0.12)	109	K1.28 (0.11)*	109	K1.42 (0.12)***	110	K1.70 (.012)***
PGI-improvement[a]	111	2.91 (0.12)	108	2.68 (0.12)	111	2.21 (0.12) ***	109	2.24 (.0.12)**
SF McGill total score[b]	96	K5.39 (0.66)	88	K7.23 (0.67)*	95	K8.25 (0.65)***	99	K9.18 (0.64)***
Dynamic Allodynia severity[b]	103	K0.08 (0.03)	99	K0.10 (0.03)	98	K0.15 (0.03)	103	K0.10 (0.03)
SF36 Health status survey[b]								
Physical	102	3.94 (0.77)	98	3.67 (0.78)	101	5.86 (0.77)	101	5.85 (0.76)
Mental	102	K1.09 (0.75)	98	0.02 (0.76)	101	0.63 (0.76)	101	1.84 (0.75)**
Bodily pain	107	10.32 (1.89)	102	13.22 (1.91)	104	18.00 (1.89)**	105	18.32 (1.88)**
General health perceptions	106	2.03 (1.61)	100	3.94 (1.63)	103	5.66 (1.62)	102	9.56 (1.62)***
Mental health	107	K2.63 (1.69)	102	0.74 (1.68)	104	2.99 (1.65)*	105	5.14 (1.62)***
Euro quality of life[b]	107	0.08 (0.02)	101	0.10 (0.02)	104	0.13 (0.02)*	105	0.13 (0.02)*
BDI[a]	79	K1.74 (0.48)	82	K2.44 (0.48)	78	K2.71 (0.49)	74	K3.11 (0.50)*
BAI[a]	80	K2.36 (0.56)	88	K2.37 (0.54)	82	K2.78 (0.56)	83	K2.50 (0.55)

*P%0.05 vs. placebo; **P%0.01 vs. placebo; ***P%0.001 vs. placebo. BPI, Brief pain inventory; CGI-Severity, Clinical Global Impressions of Severity; PGI-Improvement, patient's global impression of improvement; SF, short form; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SE, standard error.
  [a] Results from repeated measures analysis.
  [b] Results from ANCOVA; data were only collected at baseline and last visit.

Table 3
Percentage of patients showing improvement on the McGill pain questionnaire—sensory component pain descriptions

| | Placebo | | Duloxetine | | | | | |
| | | | 20 mg/d | | 60 mg/d | | 120 mg/d[a] | |
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total	96	66 (68.8)	88	74 (84.1)*	95	80 (84.2)*	99	83 (83.8)*
Throbbing	106	45 (42.5)	100	47 (47.0)	104	52 (50.0)	105	59 (56.2)
Shooting	104	41 (39.4)	101	46 (45.5)	104	56 (53.8)	105	65 (61.9)***
Stabbing	105	41 (39.0)	100	53 (53.0)	100	56 (56.0)*	105	68 (64.8)***
Sharp	103	47 (45.6)	99	54 (54.5)	102	71 (69.6)***	104	70 (67.3)**
Cramping	105	46 (43.8)	97	47 (48.5)	103	50 (48.5)	103	52 (50.5)
Gnawing	104	35 (33.7)	97	32 (33.0)	103	44 (42.7)	102	45 (44.1)
Hot-burning	104	47 (45.2)	101	59 (58.4)	103	60 (58.3)	105	66 (62.9)*
Aching	103	49 (47.6)	100	54 (54.0)	103	59 (57.3)	105	60 (57.1)
Heavy	103	41 (39.8)	99	46 (46.5)	103	51 (49.5)	104	51 (49.0)
Tender	105	48 (45.7)	100	48 (48.0)	104	52 (50.0)	105	57 (54.3)
Splitting	105	34 (32.4)	101	38 (37.6)	104	45 (43.3)	105	50 (47.6)*

*$P \% 0.05$ vs. placebo, **$P \% 0.01$ vs. placebo,***$P \% 0.001$ vs. placebo.
  [a] Bi-daily dosing administration.

the 60 mg/d group, and 57 (52%) in the 120 mg/d group. The number of patients achieving a 50% reduction in the 24-h Average Pain Score was significantly greater for all three active-treatment groups when compared with placebo ($P ! 0.05$).

The results of secondary efficacy measures are summarized in Table 2. Both duloxetine 60 and 120 mg/d treatment groups produced significantly greater improvement over placebo for all pain measures (Worst Pain, Night Pain, BPI Average Pain Severity, BPI Worst Pain Severity, BPI Least Pain Severity, BPI Pain Severity Right Now, SF-McGill total score), except dynamic allodynia. The duloxetine 60 and 120 mg/d treatment groups also demonstrated significant improvement on measures of general illness severity and improvement (CGI-Severity and PGI-Improvement). Patients treated with duloxetine 20 mg/d were significantly better than placebo on the measures of worst pain score, SF-McGill total score, and CGI-Severity.

The analysis of the individual SF-McGill sensory pain components revealed that a significantly higher percentage of duloxetine 120 mg/d patients reported improvement in shooting, stabbing, sharp, hot-burning, and splitting pain sensations when compared with placebo patients (Table 3). A significantly higher percentage of duloxetine 60 mg/d patients reported improvement in stabbing and sharp pain sensations when compared with placebo patients.

The comparison of the average daily dose of supplemental acetaminophen/analgesic use indicated that duloxetine-treated patients had reduced pain severity and required less supplemental analgesic compared with placebo. The duloxetine 60 and 120 mg/d groups used significantly less supplemental analgesic than the placebo group ($P \% 0.01$; see Fig. 5), and the duloxetine 20 mg/d group used numerically less than the placebo group ($P Z 0.080$). Baseline dynamic allodynia scores were very low indicating that most patients lacked pain induced by brush stroking and did not show significant differences across the treatments at

endpoint. Similarly, baseline depression and anxiety symptom severities, assessed by BDI and BAI, respectively, were low and the decrease in these scores across the study and differences among the treatments were not significant (see Table 2).

Most health outcomes measures, the SF-36 Health Status Survey, BPI Interference, and EQ-5D, summarized in Table 2, improved significantly more for patients treated with duloxetine 60 and 120 mg/d compared to those treated with placebo. Exceptions included the SF-36 Physical Component that lacked significant difference across treatment groups and the Mental Component and General Health Perceptions that demonstrated significantly greater improvement for duloxetine 120 mg/d treatment group compared with the placebo treatment group.

3.4. Evaluation of direct treatment effect on pain reduction

From path analysis, duloxetine 60 mg/d demonstrated a significant direct treatment effect on average pain score
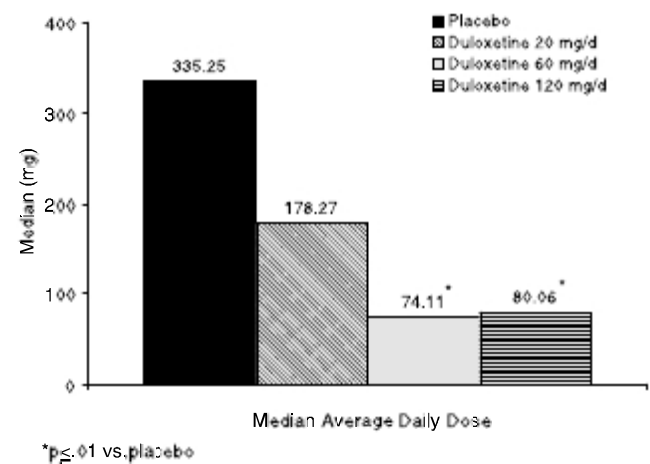

Fig. 5. Supplemental analgesic use for pain—median average daily dose.

(PZ0.003 vs. placebo). The total treatment effect of duloxetine 60 mg/d vs. placebo observed on the reduction in 24-h average pain was decomposed into three effects as follows: 94.8% direct effect, 0.2% indirect effect through improvement on mood (change in BDI), and 5.1% indirect effect through improvement on anxiety symptoms (change in BAI). For duloxetine 120 mg/d, there was no effect of improvement on the BAI on the change in the 24-h Average Pain Score. When the anxiety component was removed from the analysis, the direct treatment effect on 24-h Average Pain Score was significant (P!0.001 vs. placebo) and accounted for 88.6% of the total treatment. The indirect treatment effect through change in BDI accounted for 11.4% of the total effect.

3.5. Safety

3.5.1. Adverse events

A total of 49 (10.7%) patients discontinued due to adverse events (Fig. 3). There were group differences with the fewest discontinuations for the duloxetine 20 mg/d group (4.3%) and the most for the duloxetine 120 mg/d group (19.5%).

Treatment-emergent adverse events by treatment with a significant difference in reporting frequency from placebo are shown in Table 4. Two adverse events (somnolence and constipation) showed a significant difference between duloxetine 60 mg/d and placebo. Most adverse events were mild or moderate, except severe somnolence, which was reported significantly more frequently by the duloxetine 120 mg/d treatment group than the other treatment groups, which had no severe somnolence reports.

Some pain adverse events (back pain, arthralgia, and pruritis) were reported significantly less frequently by the duloxetine 60 and 120 mg/d groups compared with placebo. Placebo-treated patients reported significantly greater incidence of lower limb edema and peripheral swelling than duloxetine-treated patients.

Table 4

Treatment-emergent adverse events that had statistically significant differences between duloxetine 120 mg/d and placebo

	Placebo NZ115	Duloxetine		
		20 mg/d NZ115	60 mg/d NZ114	120 mg/d NZ113
Nausea	11 (9.6%)	16 (13.9%)	19 (16.7%)	31 (27.4%)***
Somnolence	9 (7.8%)	9 (7.8%)	23 (20.2%)**	32 (28.3%)***
Dizziness	8 (7.0%)	7 (6.1%)	11 (9.6%)	26 (23%)***
Constipation	4 (3.5%)	6 (5.2%)	17 (14.9%)**	12 (10.6%)*
Dry mouth	7 (6.1%)	6 (5.2%)	8 (7%)	17 (15%)*
Sweating increased	3 (2.6%)	7 (6.1%)	4 (3.5%)	10 (8.8%)*
Appetite decreased	0	3 (2.6%)	3 (2.6%)	14 (12.4%)***
Anorexia	1 (0.9%)	3 (2.6%)	3 (2.6%)	9 (8%)**
Weakness	0	1 (0.9%)	3 (2.6%)	8 (7.1%)**

*P%0.05 vs. placebo, **P%0.01 vs. placebo, ***P%0.001 vs. placebo.

A total of 19 patients experienced serious adverse events, defined as any event resulting in or prolonging hospitalization or death, life threatening experience, severe or permanent disability during the study. Among serious adverse events reported as reason for discontinuation, one death occurred due to accidental drowning in the placebo group. Serious adverse events occurring in more than one patient included chest pain (placebo: 1 [0.9%]; duloxetine 20 mg/d: 1 [0.9%]), hypergylcemia NOS (placebo: 1 [0.9%]; duloxetine 120 mg/d: 1 [0.9%]), and myocardial infarction (duloxetine 20 mg/d: 1 [0.9%]; duloxetine 120 mg/d: 1 [0.9%]). There were no significant treatment group differences in occurrence.

3.5.2. Laboratory data

Although mean changes in several laboratory analytes differed statistically significantly across treatments groups, the mean changes were small and none were considered clinically meaningful. Compared with placebo-treated patients, the duloxetine 120 mg/d group had a statistically significant mean decrease in uric acid, chloride, and gamma-glutamyl transferase (GGT), and increase in bicarbonate. The 60 mg/d group had decreases in sodium, chloride, and alanyl leucine transferase (ALT). Alkaline phosphatase showed a dose-related increase.

There were no statistically significant treatment-group differences in the incidence of treatment-emergent abnormal hematology analytes. Hematology analytes showed several statistically significant differences; however, these mean changes were not considered clinically relevant.

Duloxetine lacked adverse effects on glycemic control or lipids and, consistent with this finding, had no significant difference among treatment groups in number of hypoglycemic events (Table 5).

Table 5

Laboratory values

	Placebo NZ115	Duloxetine		
		20 mg/d NZ115	60 mg/d NZ114	120 mg/d[a] NZ113
HgbA1c[b]	K0.0004	K0.00021	K0.00039	0.00127
P-value		0.450	0.432	0.116
LDL-C[b]	K0.036	0.008	K0.034	K0.007
P-value		0.442	0.953	0.728
HDL-C[b]	K0.023	0.018	K0.004	0.018
P-value		0.075	0.239	0.102
Triglycerides[b]	K0.025	K0.090	K0.332	K0.11
P-value		0.529	0.532	0.703
Hypoglycemic episodes[c]				
Mean	0.19	0.13	0.10	0.13
SD	0.72	0.58	0.21	0.53
Median	0.00	0.00	0.00	0.00
P-value	–	0.465	0.867	0.555

P-values vs. placebo. HgbA1c, urobilinogen; LDL-C, microscopic examination of sediment; HDL-C, nitrite; SD, standard deviation.
[a] Bi-daily dosing administration.
[b] Mean change from baseline to endpoint.
[c] Weekly average number.

3.5.3. Vital signs and electrocardiographic results

The incidence of sustained hypertension was 6 (5%), 9 (8%), 1 (1%), and 3 (3%) for the duloxetine 20, 60, 120 mg/d, and placebo treatment groups, respectively. There was no difference between the duloxetine treatment groups and placebo in the percentage of cases of sustained hypertension. Compared with the placebo group, the duloxetine 60 and 120 mg/d treatment groups had a statistically significant mean decrease in QT interval (K14.25 and K11.49 ms, respectively).

4. Discussion

In this randomized, double-blind, 12-week trial, duloxetine at 60 and 120 mg/d demonstrated significantly greater efficacy than placebo on most outcome measures in the management of pain due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus. Specifically, pain reduction was significant for average pain, worst pain, least pain, night pain, and pain 'right now.' Patient- and clinician-rated global improvement scores were also significantly improved. In addition, duloxetine at 120 mg/d appeared to work best on pain described as shooting, stabbing, sharp, hot-burning, and splitting. Patients treated with duloxetine not only reported improvement on measures of pain but also used significantly less supplemental analgesic as well. Furthermore, path analysis showed that duloxetine affected pain directly rather than indirectly through mood improvement.

In addition to relieving pain, treatment with duloxetine was also associated with significant improvement in daily functioning. In particular, there was a reduction of interference with activity as measured by the BPI and improvement in quality of life, as measured by the EQ-5D scale. These effects highlight the clinical relevance of duloxetine management of DPNP.

The reduction in pain severity demonstrated in this trial is consistent with the previously reported findings that duloxetine was effective in treating pain in animal models (Iyengar et al., 2004) and extends the finding of reduced severity of painful physical symptoms in depressed patients treated with duloxetine (Detke et al., 2002a,b; Nemeroff et al., 2002). These results are also consistent with human clinical data on 5-HT/NE and known 5-HT/NE pathways that suggest targeting both pathways is better than targeting each individually (Sindrup and Jensen, 1999).

In general, duloxetine was well tolerated and safe during this 12-week study. There were more discontinuations due to adverse events in the duloxetine 60 and 120 mg/d treatment groups than in the placebo treatment group; however, only two adverse events (somnolence and constipation) were reported more frequently by the 60 mg/d treatment group than by the placebo treatment group. With regard to safety issues of central importance to patients with diabetes, duloxetine does not appear to adversely affect glycemic control, lipid profiles, or QTc interval, or show clinically relevant changes in heart rate and blood pressure (Detke et al., 2002a). The lack of significant cardiovascular changes due to duloxetine therapy in these patients suggests that duloxetine-treated patients with diabetes mellitus do not require additional cardiovascular assessments than they do for their underlying diabetes.

The efficacy of duloxetine 60 and 120 mg/d was similar in this trial, but duloxetine 60 mg/d produced fewer discontinuations for adverse events and a slightly reduced frequency of treatment-emergent adverse events. Duloxetine is currently approved by the FDA for the management of DPNP at a dose of 60 and 120 mg/d. Although the higher dose of 120 mg/d did not produce significantly greater improvement than 60 mg/d and was less well tolerated, it was safe and effective and may be an appropriate dose for patients who require additional pain relief.

The exclusion of patients with depression and anxiety by the MINI was confirmed by the low scores on the BDI and BAI. As a consequence, antidepressant or anxiolytic effects by duloxetine could not be demonstrated; however, the absence of depressive and anxiety symptoms at baseline, confirmed by the results of path analysis, indicate that analgesic effects were not dependent on improvement of mood or anxiety symptoms.

4.1. Strengths and limitations

In this trial, the patient population was limited due to exclusion of patients whose comorbid conditions and concomitant medications might have interfered with interpretation of efficacy or safety; thus, further study will be required to generalize these findings to all patients with DPNP. In addition, this condition requires prolonged therapy and evaluation for a longer duration than the 12 weeks presented. Finally, future studies with an active comparator would allow for a more complete evaluation of the benefits of duloxetine in DPNP. Strengths of the current study include the use of a randomized, prospective design, multiple clinically significant measures related to both efficacy and safety, and an adequate dose range to assess the dose–response relationship. It is also important to note that patients were not allowed to take other drugs used to treat neuropathic pain.

In sum, this study demonstrates that duloxetine is effective in managing DPNP and that this is not an indirect effect of improved mood. Presumably, this effect is due to the ability of duloxetine to enhance both 5-HT and NE function in descending modulatory pain pathways. Thus, duloxetine has a distinct efficacy in managing the persistent pain condition associated with diabetic neuropathy and efficacy in treating the emotional and painful physical symptoms associated with depression.

5. Declaration of interest

Acknowledgements

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A Double-Blind, Randomized Multicenter Trial Comparing Duloxetine with Placebo in the Management of Diabetic Peripheral Neuropathic Pain

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ABSTRACT

Objective. Assess efficacy and safety of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, on the reduction of pain severity, in patients with diabetic peripheral neuropathic pain (DPNP).

Methods. This was a multicenter, parallel, double-blind, randomized, placebo-controlled trial that enrolled 348 patients with pain due to peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. Patients (N = 116 per group) were randomly assigned to receive duloxetine 60 mg once daily (QD), duloxetine 60 mg twice daily (BID), or placebo, for 12 weeks. The primary outcome measure was the weekly mean score of 24-hour average pain severity evaluated on an 11-point Likert scale. Secondary outcome measures and safety were evaluated.

Results. Compared with placebo-treated patients, both duloxetine-treated groups improved significantly more (P < 0.001) on the 24-hour average pain score. Duloxetine demonstrated superiority to placebo in all secondary analyses of the primary efficacy measure. A significant treatment effect for duloxetine was observed in most secondary measures for pain. Discontinuations due to adverse events were more frequent in the duloxetine 60 mg BID- (12.1%) versus the placebo- (2.6%) treated group. Duloxetine showed no adverse effects on diabetic control, and both doses were safely administered and well tolerated.

Conclusions. In this clinical trial, duloxetine 60 mg QD and duloxetine 60 mg BID were effective and safe in the management of DPNP.

Key Words. Duloxetine; Diabetic Neuropathy; Pain; Antidepressant; Serotonin; Norepinephrine

Introduction

Diabetes mellitus is predicted to afflict 220 million people worldwide by the year 2010 [1]. The prevalence of diabetes in the adult U.S. population is estimated to be 7.8%, and may be as high as 12–14% in people over 40 years [2]. Approximately 30–60% of patients with diabetes develop long-term complications of peripheral neuropathy, and up to 10–20% of these patients experience pain [3–5] often described as a steady aching or burning pain and characterized by hyperalgesia, allodynia, and paresthesia [6–8].

Serotonergic and noradrenergic neurons have been implicated in the mediation of endogenous pain inhibitory mechanisms via descending inhibitory pain pathways in the brain and spinal cord [9,10]. In pathological pain states, these endogenous pain inhibitory mechanisms may be dysfunctional, contributing to the central sensitization and hyperexcitability of the spinal and supraspinal

pain transmitting pathways and manifesting as persistent pain [11]. In rodents, duloxetine has demonstrated efficacy in the formalin and capsaicin models of persistent pain, the partial sciatic nerve ligation [12], and L5/L6 spinal nerve ligation models of neuropathic pain [8]. Preclinical models of central sensitization suggest that duloxetine is effective in the treatment of persistent pain [13]. This is likely due to the effect of duloxetine on central sensitization rather than on nociception, suggested by its minimal efficacy in the tail-flick model of acute nociceptive pain. These results are indicative of pain inhibitory effects of duloxetine in the treatment of neuropathic, persistent, and inflammatory pain, but not in acute nociceptive pain. Because central sensitization and disinhibition mechanisms are believed to be involved in the development and maintenance of chronic neuropathic pain, including diabetic peripheral neuropathic pain (DPNP), duloxetine was considered to be a good clinical candidate for evaluating treatment of DPNP.

Duloxetine hydrochloride (Cymbalta®) is a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor that is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition [14] and it is the first U.S. Food and Drug Administration (FDA)-approved drug for the management of DPNP. In a randomized, controlled, 12-week trial comparing duloxetine 60 mg once daily (QD) and duloxetine 60 mg twice daily (BID) or 20 mg QD with placebo in the management of 477 patients [15] with DPNP and without depression, duloxetine was found to be effective and safe for DPNP management. Based on this evidence [15], two more independent studies were conducted to assess the safety and efficacy of duloxetine 60 mg QD and 60 mg BID in the management of patients with DPNP. The first of these two studies [16] confirmed findings reported earlier [15], and the second study is reported here.

Methods

Overview

Enrollment for this study extended from November 2003 to March 2004 and was conducted in 26 centers worldwide. This was a Phase III, multicenter, parallel, double-blind, randomized, placebo-controlled trial. The study protocol was approved in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent.

Entry Criteria

Patients were eligible for the study if they were ≥18 years, and presented with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus. The pain had to begin in the feet and with relatively symmetrical onset. The daily pain must have been present for at least 6 months, and the diagnosis was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI). Patients had to have a mean score of ≥4 when assessed for 24-hour average pain severity on the 11-point Likert scale (from the patient diary prior to randomization), and stable glycemic control. Patients were excluded if they were pregnant or breastfeeding, had prior renal transplant or current renal dialysis, or had a serious or unstable illness, symptomatic peripheral vascular disease, or other medical condition or psychological conditions that might compromise participation in the study. Patients were also excluded if they had a current (≤1 year) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [17] Axis I diagnosis of major depressive disorder (MDD), dysthymia, generalized anxiety disorder, alcohol, or eating disorders as determined by the Mini International Neuropsychiatric Interview (MINI) [18], or if they had a DSM-IV diagnosis or a previous diagnosis of mania, bipolar disorder, or psychosis. Other exclusion criteria included historical exposure to drugs known to cause neuropathy, history of substance abuse or dependence within the previous year (excluding nicotine and caffeine), a positive urine drug screen for any substances of abuse or excluded medication, or a history of a medical condition including pernicious anemia and hypothyroidism that could have been responsible for neuropathy, and treatment with a monoamine oxidase inhibitor (MAOI) or fluoxetine within 30 days of randomization. Patients were excluded if they had severe allergic reactions to multiple medications, and prior participation in a study of duloxetine.

Concomitant medication exclusions included chronic use of antidepressants, antiemetics, analgesics with the exception of acetaminophen up to 4 g/day and aspirin up to 325 mg/day. Antimanics, antimigraine medications, antipsychotics, benzodiazepines, capsaicin, chloral hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psychostimulants, oral and injectable steroids, and anticonvulsants were excluded. Concomitant medication inclusions (chronic and episodic) were antacids, antiasthma agents, aminophylline, birth

control medication, cough/cold preparations (that did not contain dextromethorphan), diuretics, inhaled and topical steroids, hypoglycemics, insulin, laxatives, theophylline, anticoagulants, antibiotics, antidiarrheals, and antihistamines. Medications including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor agonists, antiarrythmics, anticoagulants, calcium channel blockers, and others were allowed provided the patient had been on a stable dose for 3 months prior to enrollment.

Study Design

This study was designed to enroll 330 patients to three treatment groups. With 110 patients per arm, the study had at least 90% power to detect a treatment-group difference of −1.20 points in the baseline-to-endpoint mean change on the weekly mean of 24-hour average pain severity between duloxetine 60 mg BID and placebo treatment groups. The sample size was determined using a two-sided test with $\alpha = 0.05$, and assuming a common standard deviation of 2.2 and a discontinuation rate of 35%.

Patients who met entry criteria following an up to 3-week screening phase (study period I) were randomized to treatment with duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo, with randomization performed at visit 3 in a 1:1:1 ratio. Assignment to treatment groups was determined by a computer-generated random sequence using an Interactive Voice Response System. Patients received either of (or a combination of, depending on their randomly assigned treatment) the following: 30 mg capsules of duloxetine hydrochloride or placebo capsules identical to duloxetine capsules. Patients randomly assigned to all treatment groups were instructed to take two capsules (by mouth) every morning and every evening. Study period II consisted of a 12-week, double-blind acute therapy period and 1-week study drug tapering period. Visits to the site occurred weekly for the first 2 weeks, biweekly for the next 10 weeks, and then weekly for the next week. All patients randomized to duloxetine treatment were treated initially with 60 mg QD. After 3 days, those patients randomized to the 60 mg BID treatment group received 60 mg BID. Patients in the 60 mg QD treatment group continued at 60 mg QD. At Visit 2 (week prior to randomization) through Visit 10 (week 12), patients received a diary and at Visit 3 through Visit 10 (week 12), patients received study drug. At Visit 10, the patient's study drug dose was halved to 30 mg QD and 60 mg QD

for the duloxetine 60 mg QD- and 60 mg BID-treated group, respectively. The efficacy and safety evaluation of duloxetine versus placebo was conducted using data from the 12-week acute therapy period where duloxetine 60 mg was administered at a full dosage.

Efficacy Measures

The primary efficacy measure was the change in the weekly mean of the 24-hour average pain scores (referred to as the 24-hour average pain score) as measured by an 11-point Likert scale that was completed daily by the patients in a diary. At Visit 2, site personnel dispensed daily diaries and educated patients on proper completion of the diary. The mean score in a week was determined by averaging the daily scores (among the days in the week) on the 24-hour average pain collected from the diary. Overall study diary compliance was defined as being compliant at each visit in the study period from Visit 4 through Visit 10. A patient was considered to be compliant with the diary at a certain visit if the patient completed at least 80% of the diary over the total days since the last visit. Scores for 24-hour average pain, worst pain, and night pain were derived from the patient diary collected at each visit. Protocol-specified response at endpoint was defined as a 30% reduction from baseline to endpoint in the 24-hour average pain score. Responses based on 50%, 75%, and 100% reductions from baseline were also reported. Sustained response at endpoint was defined as a 30% reduction from baseline to endpoint in the 24-hour average pain severity with a 30% reduction from baseline at a week at least 2 weeks prior to the last, and with at least a 20% reduction from baseline at every week in between.

Secondary efficacy measures for pain were the weekly mean of daily worst pain and night pain on the 11-point Likert scale (collected from patient's diary), Brief Pain Inventory (BPI) [19], the Short-Form McGill Pain Questionnaire (sensory portion) (SF-MPQ) [20] (sum of 11 pain descriptor terms—throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting; the pain intensity for each pain descriptor was rated on a scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe), and dynamic allodynia. Dynamic allodynia was assessed by the clinician using a brush stroke (to the same body location at baseline and endpoint) to elicit pain severity from the patient. The patient was asked to answer whether a brush swept over

the skin caused pain. The score range was from a scale of 0 (no pain) to 3 (severe pain). The interference portion of the BPI was completed by the patient to measure how much pain had interfered with patient outcomes. Other secondary measures included the 17-item Hamilton Depression Rating Scale (HAMD$_{17}$) [21,22], the Clinical Global Impression of Severity (CGI-Severity) scale [23], and Patient Global Impression of Improvement (PGI-Improvement) scale. The average daily intake of acetaminophen taken for DPNP was recorded.

Schedule of Assessments

The screening portion of the protocol (Visits 1–3) included the medical history and the MINI [18] to determine whether patients met criteria for excluded primary DSM-IV Axis I diagnoses. Patients also underwent a physical exam, electrocardiogram (ECG), and laboratory tests. At randomization (Visit 3), and at each subsequent visit the diary was collected, vital signs were checked, and adverse events and concomitant medication were reviewed. BPI and CGI-Severity were completed at Visits 3, 6, 8, and 10. The PGI-Improvement was measured at Visits 6, 8, and 10. The HAMD$_{17}$, SF-MPQ, and dynamic allodynia were measured at Visits 3 and 10.

Safety Assessments

Safety was evaluated by measuring discontinuation rates, treatment-emergent adverse events (TEAEs), serious adverse events, vital signs, weight, laboratory analyses, ECGs, frequency of significant hypoglycemic events, and electrophysiology assessments.

Statistical Analysis

All analyses were conducted on an intent-to-treat basis. Treatment effects were evaluated based on a two-sided significance level of 0.05, and interaction effects at 0.10. The change from baseline to endpoint (the last nonmissing observation after randomization) on the continuous efficacy measures was analyzed using an analysis of covariance (ANCOVA) model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline scores. When the interaction was not statistically significant, the treatment-group contrasts were made from the model without interaction. Type II sum-of-squares for the least-squares means were used. Repeated measure analysis [24] was used as the secondary methodology to dem-

onstrate the invariance of the results and the time course of the treatment effect. The model included terms of the treatment, investigator, visit, and treatment-by-visit interaction, as well as the covariate of baseline score and baseline-by-visit interaction. The unstructured covariance was used in the model, and the analysis was implemented using SAS PROC MIXED. An analysis of variance (ANOVA) model with the terms of treatment and investigator was used to analyze the continuous safety measures or the corresponding rank-transformed data (labs and daily average of concomitant acetaminophen use). Proportions were analyzed using Fisher's exact test. Time to first response (30% reduction from baseline) and time to the first visit where sustained response was observed were analyzed by a log-rank test.

Path analysis [25,26] was used to assess the direct treatment effect on pain reduction after accounting for the possible treatment effect on mood. This analysis tested the null hypothesis that change in the 24-hour average pain score depended on change of mood, as measured by HAMD$_{17}$ total score, versus the alternative that the reduction in 24-hour average pain score was due to a direct analgesic effect of the treatment and was independent of the treatment effect on mood.

Throughout the article, the term "significant" indicates statistical significance, and "mean change" refers to "least-squares mean change."

Results

Patient Disposition

A total of 475 patients were screened to enroll 348 patients who met entry criteria and were randomly assigned to duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo (116 patients in each group). Fifty-two (15%) patients withdrew for all reasons during the acute therapy phase, 15 (13%) from the duloxetine 60 mg QD group, 21 (18%) from the duloxetine 60 mg BID group, and 16 (14%) from the placebo group. Twenty-two (6.3%) patients discontinued due to adverse events, 5 (4.3%) from the duloxetine 60 mg QD group ($P = 0.72$ vs placebo), 14 (12.1%) from the duloxetine 60 mg BID group ($P = 0.01$ vs placebo), and 3 (2.6%) from the placebo group.

Baseline Clinical and Demographic Characteristics

The majority of the patients in the study were Caucasian (99.7%) with a mean age of 58.8 years (Table 1). The mean duration of diabetes was 13.8 years. Type 2 diabetes was the most prevalent

Table 1 Demographics and baseline assessments

Variable	Placebo (N = 116)	Duloxetine 60 mg QD (N = 116)	Duloxetine 60 mg BID (N = 116)	Total (N = 348)	P Value
Age, years,* mean (SD)	59.2 (9.8)	58.3 (10.9)	59.0 (9.6)	58.8 (10.1)	0.711
Gender,[†] N (%)					0.237
Female	63 (54.3)	68 (58.6)	55 (47.4)	186 (53.4)	
Race (origin),[†] N (%)					>0.999
Caucasian	116 (100)	115 (99.1)	116 (100)	347 (99.7)	
East/Southeast Asian	0	1 (0.9)	0	1 (0.3)	
Weight, kg,* mean (SD)	87.2 (16.5)	83.3 (19.6)	87.1 (19.2)	85.9 (18.5)	0.128
Type of diabetes mellitus,[†] N (%)					0.269
Type 1	14 (12.1)	23 (19.8)	17 (14.7)	54 (15.5)	
Type 2	102 (87.9)	93 (80.2)	99 (85.3)	294 (84.5)	
Duration of diabetes, years,* mean (SD)	12.8 (8.6)	14.6 (8.9)	13.9 (9.7)	13.8 (9.1)	0.372
Duration of DN, years,* mean (SD)	4.0 (3.5)	4.5 (4.4)	4.5 (4.6)	4.3 (4.2)	0.570
MNSI,* mean (SD)	5.2 (1.6)	4.9 (1.4)	4.8 (1.4)	5.0 (1.5)	0.036
Pain severity at baseline,* mean (SD)					
24-hour average pain severity	5.5 (1.3)	5.5 (1.1)	5.7 (1.3)	5.6 (1.2)	0.542
24-hour worst pain severity	6.5 (1.4)	6.7 (1.3)	6.9 (1.3)	6.7 (1.4)	0.213
Night pain severity	6.2 (1.7)	5.9 (1.7)	6.1 (1.6)	6.1 (1.7)	0.523
Mood and general illness at baseline,* mean (SD)					
HAMD$_{17}$ total score	3.8 (3.2)	3.8 (3.7)	4.2 (3.1)	3.9 (3.3)	0.608
CGI-Severity	4.5 (0.9)	4.6 (0.9)	4.5 (1.0)	4.5 (0.9)	0.563

* Means were analyzed using a Type III Sum of squares analysis of variance.
[†] Frequencies were analyzed using a Fisher's exact test.
QD = once a day; BID = twice daily; SD = standard deviation; BPI = Brief Pain Inventory; CGI-Severity = Clinical Global Impressions of Severity; DN = diabetic neuropathy; MNSI = Michigan Neuropathy Screening Instrument; HAMD$_{17}$ = 17-item Hamilton Depression Rating Scale.

(84.5%), and the mean MNSI score at the time of screening was 5.0. At baseline, there was a significant difference between treatment groups for the MNSI score, with placebo-treated patients having a slightly higher score ($P = 0.036$). At baseline, the mean dynamic allodynia score was 0.38 and HAMD$_{17}$ total score was 3.89.

Efficacy
In the mean change analyses, duloxetine 60 mg QD and 60 mg BID were statistically superior to placebo on the primary and all secondary measures (Table 2) except for HAMD$_{17}$ total score and dynamic allodynia. After adjusting for the baseline MNSI score, the P value for the primary analysis did not change. There was no significant difference in efficacy measures between duloxetine 60 mg QD and 60 mg BID. The repeated measure analysis showed that duloxetine was significantly superior to placebo beginning 1 week after randomization and continuing through the study in the analyses of the 24-hour average pain (Figure 1), worst pain severity, and night pain scores. Duloxetine was significantly better than placebo in reducing BPI Severity scores for worst pain, least pain, average pain, and pain right now using both mean change analysis and repeated measure analysis (Figure 2). There were no statistically significant differences among treatment groups for study diary compliance.

Both duloxetine groups were superior to placebo on CGI-Severity and PGI-Improvement scores, and demonstrated an improvement in the total score of the sensory component of the SF-MPQ. The 24-hour average pain severity response rate at endpoint showed significant superiority for both duloxetine 60 mg QD (68.14%, $P < 0.001$) and duloxetine 60 mg BID (64.04%, $P = 0.002$) compared with placebo (43.36%). A 50%, 75%, and 100% reduction in the 24-hour average pain response rate at endpoint was achieved by 30%, 11%, and 4% of patients, respectively, in the placebo group, 50%, 20%, and 5% of patients, respectively, in the duloxetine 60 mg QD group, and 39%, 22%, and 8% of patients, respectively, in the duloxetine 60 mg BID group. Duloxetine 60 mg QD (60.18%, $P = 0.002$) and duloxetine 60 mg BID (57.02%, $P = 0.008$) also demonstrated significant superiority to placebo (38.94%) at achieving sustained response at endpoint. Compared with placebo, patients in both of the duloxetine treatment groups achieved first response and sustained response in a significantly shorter amount of time ($P < 0.001$).

The path analysis for the 24-hour average pain score showed that the direct treatment effect of duloxetine on pain accounted for the major portion of the total effect (98.0% and 92.7% for duloxetine 60 mg BID and 60 mg QD vs placebo, respectively).

Table 2 Mean change in efficacy measures

Measure (Score Range)	Placebo		Duloxetine 60 mg QD			Duloxetine 60 mg BID		
	N	Mean Change (SE)	N	Mean Change (SE)	Between-Group Difference (95% CI) Versus Placebo	N	Mean Change (SE)	Between-Group Difference (95% CI) Versus Placebo
Weekly mean score from patients diary								
24-hour average pain score	113	−1.60 (0.18)	113	−2.50 (0.18)***	−0.90 (−1.39, −0.42)	114	−2.47 (0.18)***	−0.87 (−1.36, −0.39)
24-hour worst pain score	113	−2.03 (0.20)	113	−2.97 (0.20)***	−0.95 (−1.51, −0.39)	114	−2.84 (0.20)**	−0.81 (−1.37, −0.25)
Night pain score	113	−1.87 (0.19)	113	−2.81 (0.19)***	−0.94 (−1.46, −0.41)	114	−2.78 (0.19)***	−0.92 (−1.45, −0.38)
BPI Severity								
Average pain	109	−1.82 (0.19)	108	−2.65 (0.19)**	−0.84 (−1.36, −0.32)	108	−2.62 (0.19)**	−0.81 (−1.33, −0.28)
Worst pain	109	−2.20 (0.22)	108	−3.00 (0.22)*	−0.80 (−1.41, −0.19)	108	−3.09 (0.22)**	−0.89 (−1.50, −0.28)
Least pain	109	−1.17 (0.18)	108	−1.98 (0.18)**	−0.80 (−1.30, −0.31)	108	−1.86 (0.18)**	−0.69 (−1.19, −0.19)
Pain right now	109	−1.48 (0.21)	108	−2.25 (0.21)**	−0.77 (−1.34, −0.19)	108	−2.56 (0.21)***	−1.08 (−1.66, −0.50)
CGI Severity	113	−0.93 (0.09)	110	−1.42 (0.09)***	−0.49 (−0.75, −0.23)	109	−1.40 (0.10)***	−0.47 (−0.74, −0.20)
SF-MPQ total score	101	−4.96 (0.60)	102	−7.47 (0.61)**	−2.51 (−4.20, −0.82)	104	−7.82 (0.61)***	−2.86 (−4.54, −1.17)
PGI Improvement†	112	3.04 (0.10)	109	2.50 (0.10)***	−0.53 (−0.81, −0.26)	111	2.54 (0.10)***	−0.49 (−0.77, −0.21)
Hamilton depression rating scale	101	−0.55 (0.25)	103	−1.17 (0.25)	−0.62 (−1.32, 0.07)	100	−0.65 (0.25)	−0.10 (−0.80, 0.60)
Dynamic allodynia	108	−0.14 (0.04)	108	−0.22 (0.04)	−0.08 (−0.19, 0.02)	108	−0.14 (0.04)	−0.00 (−0.10, 0.10)
BPI Interference								
General activity	109	−1.38 (0.22)	108	−2.22 (0.22)**	−0.84 (−1.46, −0.23)	108	−2.39 (0.22)**	−1.01 (−1.63, −0.39)
Mood	109	−1.76 (0.20)	108	−2.32 (0.20)	−0.56 (−1.12, 0.01)	108	−2.60 (0.20)**	−0.84 (−1.40, −0.28)
Walking ability	108	−1.51 (0.22)	108	−2.50 (0.21)**	−0.99 (−1.59, −0.40)	108	−2.68 (0.22)***	−1.17 (−1.77, −0.56)
Normal work	109	−1.45 (0.20)	108	−2.24 (0.20)**	−0.78 (−1.35, −0.21)	108	−2.46 (0.21)***	−1.01 (−1.58, −0.43)
Relationships	108	−1.19 (0.18)	108	−1.56 (0.18)	−0.37 (−0.86, 0.13)	108	−1.78 (0.18)*	−0.59 (−1.09, −0.10)
Sleep	108	−2.25 (0.24)	108	−3.30 (0.23)**	−1.04 (−1.70, −0.39)	107	−3.00 (0.24)*	−0.75 (−1.41, −0.08)
Enjoyment of life	109	−1.79 (0.22)	108	−2.63 (0.22)**	−0.83 (−1.44, −0.23)	108	−2.64 (0.22)**	−0.84 (−1.44, −0.25)
Average of seven questions	109	−1.56 (0.18)	108	−2.43 (0.18)***	−0.88 (−1.38, −0.38)	108	−2.54 (0.18)***	−0.98 (−1.49, −0.47)

* $P < 0.05$ versus placebo; ** $P < 0.01$ versus placebo; *** $P < 0.001$ versus placebo.
† Least square means at endpoint.
BPI = Brief Pain Inventory; CGI = Clinical Global Impressions; PGI = Patient's Global Impression; SE = standard error; SF-MPQ = Short-Form McGill Pain Questionnaire; CI = confidence interval; QD = once daily; BID = twice daily.
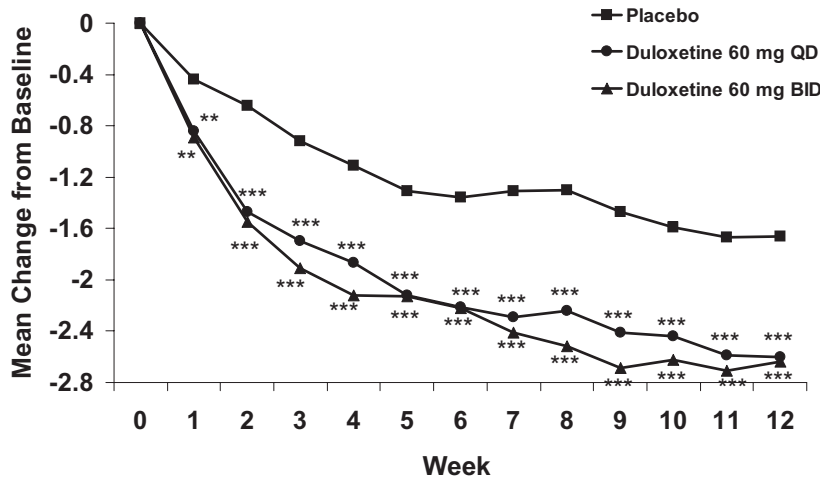
Figure 1 Mean change in 24-hour average pain severity score. $**P \leq 0.01$ versus placebo; $***P \leq 0.001$ versus placebo.

The mean average daily dose for concomitant use of acetaminophen for DPNP (placebo-treated group: 202.52 mg, duloxetine 60 mg QD-treated group: 151.88 mg, duloxetine 60 mg BID-treated group: 121.65 mg) indicated significant treatment-group differences between duloxetine 60 mg BID and placebo ($P = 0.040$). The mean change analysis of 24-hour average pain
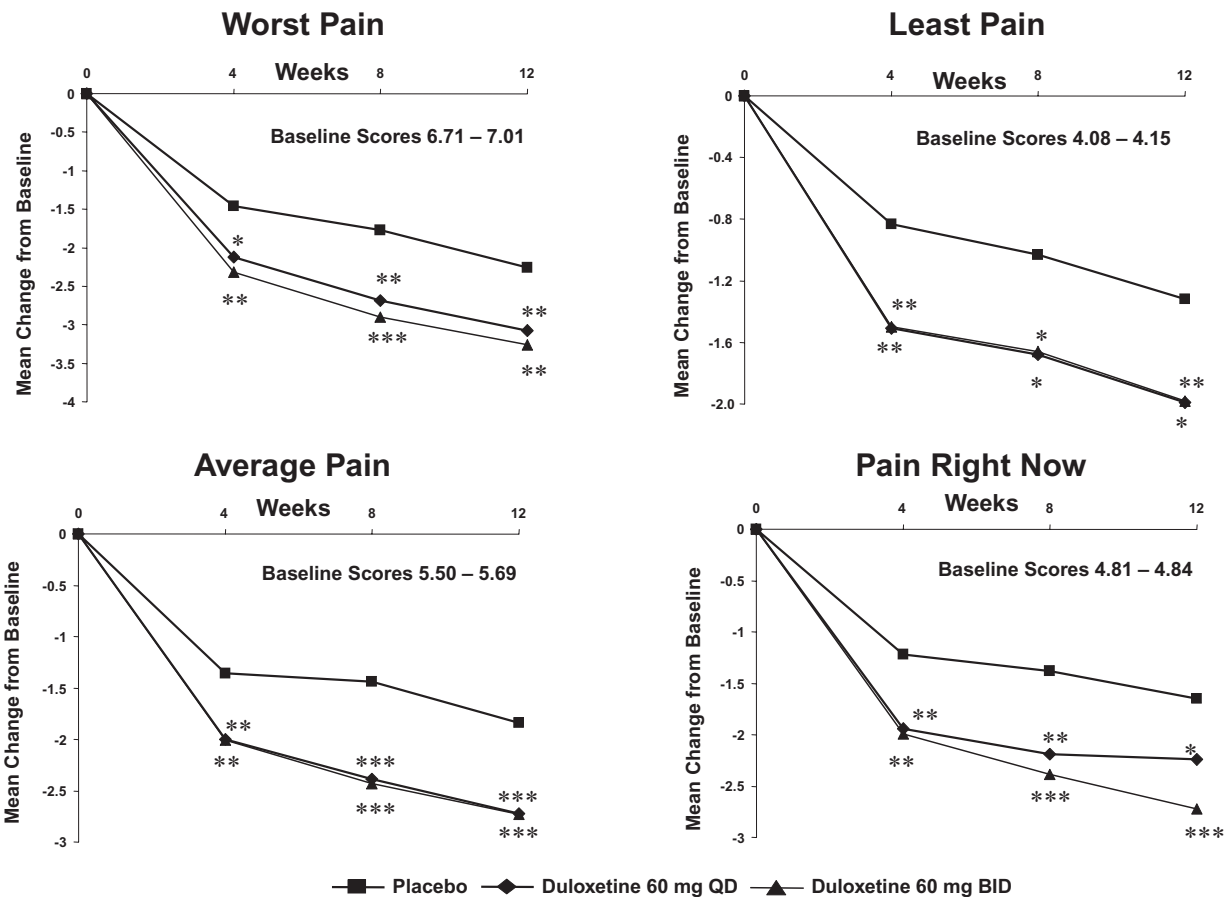

Figure 2 Brief Pain Inventory individual severity score. $*P \leq 0.05$ versus placebo; $**P \leq 0.01$ versus placebo; $***P \leq 0.001$ versus placebo.

adjusted for the concomitant acetaminophen use still showed significant superiority of both duloxetine groups to the placebo group.

In the BPI Interference scale, both duloxetine doses were significantly superior to placebo at reducing scores in all measures ($P < 0.05$), except relationship with other people item ($P = 0.146$) and mood item ($P = 0.053$) for 60 mg QD-treated patients (Table 2).

Safety

Of the 348 randomly assigned patients, 57 (49.1%) placebo-, 71 (61.2%) duloxetine 60 mg QD- ($P = 0.086$ vs placebo), and 73 (62.9%) duloxetine 60 mg BID- ($P = 0.047$ vs placebo) treated patients reported at least one TEAE. Patients in both duloxetine groups reported treatment-emergent nausea, somnolence, hyperhidrosis, and anorexia significantly more frequently than placebo-treated patients. Additionally, vomiting and constipation were reported by duloxetine 60 mg BID-treated patients significantly more frequently than placebo-treated patients. Twenty-two patients discontinued during the therapy phase due to adverse events (duloxetine 60 mg QD, 5 [4.3%]; duloxetine 60 mg BID, 14 [12.1%]; placebo 3 [2.6%]), with significant differences between duloxetine 60 mg BID- and placebo-treated groups ($P = 0.010$). Eighty-six percent of patients who discontinued due to adverse events did so during the first 4 weeks of the study. Vomiting (3.4%) and nausea (1.7%) were reported as reasons for discontinuation in >1% of duloxetine 60 mg BID-treated patients. Ten (2.9%) patients experienced 13 serious adverse events with no significant treatment-group differences. These included 4 (3.4%) placebo-treated patients (events: anemia, cerebrovascular accident, chest pain, chronic obstructive airways, dyspnea, melaena, pneumonia), 4 (3.4%) duloxetine 60 mg QD-treated patients (events: atrial fibrillation, cholecystitis, diabetes mellitus, nephrolithiasis), and 2 (1.7%) duloxetine 60 mg BID-treated patients (events: urinary calculus, ventricular extrasystoles). The weekly average of significant hypoglycemic events showed no significant differences between treatment groups.

Duloxetine 60 mg QD-treated patients experienced a mean increase in alkaline phosphatase, aspartate transaminase/serum glutamic oxaloacetic transaminase, inorganic phosphorous, fasting glucose, and uric acid compared with placebo-treated patients. Duloxetine 60 mg BID-treated patients experienced a mean increase in cholesterol, alkaline phosphatase, low-density lipoprotein cholesterol, and bicarbonate HCO_3, and a mean decrease in urea nitrogen compared with placebo treated patients. These mean differences were transient, and generally of low magnitude and not considered to be clinically relevant. There were no significant treatment-group differences observed in any of the mean change analyses of electrophysiology measures.

There was a slight but significant mean decrease in weight from baseline to endpoint for duloxetine 60 mg BID- (mean change [SD]: -0.90 kg [2.39]; $P = 0.006$) treated patients compared with placebo-treated patients. There was a significant mean increase in heart rate from baseline to endpoint for duloxetine 60 mg BID- (mean change [SD] beats/minute: 4.22 [10.72]; $P = 0.005$ vs duloxetine 60 mg QD; $P < 0.001$ vs placebo) treated patients compared with duloxetine 60 mg QD- (mean change [SD]: 0.47 [9.02]), and placebo- (mean change [SD]: -0.82 [10.97]) treated patients. These changes were not of clinically relevant magnitude. There were no significant treatment-group differences in mean change of systolic and diastolic blood pressure. Seventeen patients (7 [6.1%] placebo-, 4 [3.5%] duloxetine 60 mg QD-, and 6 [5.2%] duloxetine 60 mg BID-treated) experienced sustained elevation of blood pressure (defined as a sitting diastolic blood pressure ≥85 mm Hg and an increase from baseline of at least 10 mm Hg, or sitting systolic blood pressure ≥130 mm Hg and an increase from baseline of at least 10 mm Hg, for three consecutive visits), but the treatment-group differences were not significant.

Placebo-treated patients experienced mean increases in QT interval and PR interval compared with duloxetine 60 mg BID-treated patients who experienced mean decreases in QT interval (mean change [SD]: -10.44 [25.76]; $P < 0.001$) and PR interval (mean change [SD]: -4.14 [14.81]; $P = 0.006$).

Twenty-three of the 348 patients reported at least one adverse event that emerged during the 1-week drug taper phase (7 [6.0%] duloxetine 60 mg BID-treated group, 8 [6.9%] duloxetine 60 mg QD-treated group, and 8 [6.9%] placebo-treated group, all events reported in <1% of patients except hypertension [1.7%] in duloxetine 60 mg BID-treated patients), with no significant treatment-group differences in the overall incidence of taper-emergent adverse events or in any single taper-emergent adverse event.

Discussion

In this randomized, double-blind, 12-week trial, duloxetine at doses of 60 mg QD and 60 mg BID had significantly greater efficacy than placebo on most outcome measures in the management of patients with DPNP. Compared with placebo, both doses of duloxetine significantly reduced pain, beginning in the first week of management and continuing throughout the 12 weeks of therapy. Response rates demonstrated greater pain reduction for both duloxetine groups compared with placebo, and patients in the duloxetine groups were more likely to achieve a sustained response over time. Farrar et al. 2001 [27] analyzed the pooled results of 10 placebo-controlled studies involving patients with chronic pain syndromes (diabetic neuropathy, postherpetic neuralgia, chronic low back pain, fibromyalgia, and osteoarthritis) in order to corroborate the association between change in pain intensity numeric rating scale and an improvement in quantifiable measures of clinical status. Their results indicate that on average a reduction of approximately two points from baseline on an 11-point pain rating scale (shown to be equivalent to a 30% reduction on pain severity from baseline) corresponds to a clinically meaningful improvement. In this study, the 24-hour average pain severity was reduced about two points and the response rate (defined as 30% reduction from baseline to endpoint) showed significant superiority for both duloxetine 60 mg QD and duloxetine 60 mg BID compared with placebo. Significant pain reduction was observed on the 24-hour worst, and night pain scores, respectively, thus stressing the clinical relevance of duloxetine in the management of DPNP.

A significant treatment effect was observed for both duloxetine treatment groups for most BPI Interference items. Duloxetine was not statistically superior to placebo on the $HAMD_{17}$ total score and dynamic allodynia. Given the dynamic allodynia rating at baseline of less than 1 on a scale of 0–3, the patients did not have much room for improvement on this measure.

Duloxetine is known to be an effective antidepressant, raising the question as to how much of the pain reduction effect may be attributed to relief of depressive symptoms, and what would be the impact on mood when the drug was used for the management of pain on patients who do not have MDD. The potential confounding relationship between pain and mood was recognized when this study was designed, which is why patients with a clinical diagnosis of depression were excluded. This does not preclude the possibility that patients had subclinical depression. Thus, $HAMD_{17}$ was used to measure the mood change in the trial and the change in $HAMD_{17}$ was taken into account for the evaluation of pain reduction by the path analysis. A $HAMD_{17}$ score of ≤ 7 is often used as an indicator of remission in the MDD population. In this study, since patients with a clinical diagnosis of depression were excluded, the $HAMD_{17}$ score at baseline was low (3.89) and well below the standard remission criterion. This might explain the lack of an antidepressant effect observed in this study. The path analysis showed that the reduction of pain was a direct treatment effect on pain modulation, and cannot be attributed to an antidepressant effect. In addition, the analyses on $HAMD_{17}$ total showed that the mean changes from baseline to endpoint were very similar between duloxetine-treated patients and placebo-treated patients, which suggests that duloxetine has a neutral effect on mood for those patients who do not have clinically diagnosed MDD.

Duloxetine is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition [14]. These results confirm findings from previous studies where duloxetine 60 mg QD and 60 mg BID demonstrated superiority over placebo in improving DPNP [15,16], and are consistent with data that suggest that drugs with inhibition of 5-HT and NE reuptake are effective in the management of DPNP [28]. These results are also consistent with findings that duloxetine is effective in treating pain in animal models [13] and in reducing severity of painful physical symptoms in depressed patients [29–31]. Since noradrenergic and serotonergic neurons modulate the endogenous pain inhibitory pathways [9,10], the ability of duloxetine to exert its effects on both these neurotransmitter systems may explain its effectiveness in this clinical trial.

In the present study, there were no significant differences between the duloxetine 60 mg QD and duloxetine 60 mg BID treatment groups in efficacy outcomes. However, the study was not adequately powered to detect a difference between duloxetine 60 mg QD and duloxetine 60 mg BID treatment groups. Patients treated with duloxetine 60 mg BID took significantly less concomitant acetaminophen during the study than placebo-treated patients, and this finding provided some evidence of additional efficacy of duloxetine 60 mg BID.

Both doses of duloxetine were well tolerated by most patients and safely administered. Significantly more duloxetine 60 mg BID-treated patients than placebo-treated patients reported TEAEs, but these events were generally mild to moderate in severity. Although 17 patients had sustained elevation in blood pressure, several factors may explain this rate. The majority of patients (73.6%) were known to have hypertension as a secondary condition, and 7.2% of patients were known to have diabetic nephropathy, which predisposed them to elevated blood pressure. Although observed, sustained elevations in blood pressure were not likely to result from duloxetine use, as four placebo- versus one duloxetine 60 mg QD- and two duloxetine 60 mg BID-treated patients experienced sustained elevation in blood pressure. Duloxetine treatment did not result in QTc prolongation. The lack of significant cardiovascular changes due to duloxetine therapy in these patients and other studies [29,30,32,33] suggests that patients with diabetes mellitus do not require more intensive assessment of their cardiovascular status when treated with duloxetine than they require for their underlying diabetes. There were no treatment-group differences in any of the electrophysiology measures of nerve function, indicating that the reduction in pain was not related to deterioration of nerve function. Clinical laboratory assessments, vital signs, and physical findings were stable relative to baseline and no clinically relevant differences were detected between treatment groups.

Significantly more patients in the duloxetine 60 mg BID group than the placebo group discontinued treatment due to adverse events. Most patients who discontinued due to adverse events did so within the first 4 weeks of the study. This could be due to the titration of duloxetine in which patients were started on 60 mg QD and underwent titration to 60 mg BID over just 3 days, suggesting that some patients would have better tolerability with a lower duloxetine starting dose and slower titration.

Several limitations of this study should be considered. The results are based on an acute treatment trial of 12 weeks, and may not generalize to a longer duration of treatment, and DPNP, a chronic condition, likely requires management for more than 12 weeks. Further evaluation of the long-term efficacy of duloxetine on DPNP would be required to assess the effects on progression of neuropathy. Since patients were selected from among those with very limited or stable medical conditions, and stable doses of concomitant medications, the generalizability of the results to typical outpatients is limited.

In summary, this randomized, placebo-controlled study provides substantial evidence and confirms previously reported findings that treatment with duloxetine 60 mg QD and 60 BID for up to 12 weeks is safe and effective in the management of DPNP.

Acknowledgments

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A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain

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Abstract—*Background:* Serotonin (5-HT) and norepinephrine (NE) are involved in pain modulation via descending inhibitory pathways in the brain and spinal cord. *Objective:* To assess the efficacy of duloxetine, a dual reuptake inhibitor of 5-HT and NE, on the reduction of pain severity, as well as secondary outcome measures in patients with diabetic peripheral neuropathic pain (DPNP). *Methods:* In this double-blind study, patients with DPNP and without comorbid depression were randomly assigned to treatment with duloxetine 60 mg once daily (QD), duloxetine 60 mg twice daily (BID), or placebo for 12 weeks. The primary outcome measure was the weekly mean score of 24-hour average pain severity on the 11-point Likert scale. Secondary measures and health outcome measures were also assessed. *Results:* Duloxetine 60 mg QD and 60 mg BID demonstrated improvement in the management of DPNP and showed rapid onset of action, with separation from placebo beginning at week 1 on the 24-hour average pain severity score. For all secondary measures for pain (except allodynia), mean changes showed an advantage of duloxetine over placebo, with no significant difference between 60 mg QD and 60 mg BID. Clinical Global Impression of Severity and Patient's Global Impression of Improvement evaluation demonstrated greater improvement on duloxetine- vs placebo-treated patients. Duloxetine showed no notable interference on diabetic controls, and both doses were safely administered. *Conclusions:* This study confirms previous findings that duloxetine at 60 mg QD and 60 mg BID is effective and safe in the management of diabetic peripheral neuropathic pain.

Diabetes mellitus is a condition that is often associated with painful neuropathy. Diabetes affects approximately 17 million people in the United States, and it has been predicted that 220 million people worldwide will be afflicted by 2010.[1] The lifetime incidence of distal neuropathy was estimated to be 37% to 45% for patients with type 2 diabetes and 54% to 59% for patients with type 1 diabetes.[2] Patients often report superficial pain presenting as allodynia, sharp, stabbing, or burning pain in the feet, numbness, and tingling.[3] Various agents have been evaluated in randomized controlled clinical trials and are currently used to treat diabetic peripheral neuropathic pain (DPNP). These include tricyclic antidepressants (TCAs) such as amitriptyline,[4] imipramine,[5] and desipramine,[6] believed to potentiate CNS activity of serotonin (5-HT) and norepinephrine (NE) projections in nociceptive modulatory circuits,[7] and certain anticonvulsants such as gabapentin.[8] However, these drugs are often limited by their anticholinergic, α-adrenergic-blocking, and CNS side effects.

Both noradrenergic and serotonergic neurons are involved in modulating nociceptive transmission in the brain and spinal cord,[9,10] thereby indicating that they modulate the endogenous pain inhibitory pathways. An imbalance in these inhibitory mechanisms may contribute to the central sensitization and hyperexcitability of the spinal and supraspinal pain transmitting pathways. This imbalance may manifest as persistent pain[11] similar to that experienced by patients with DPNP.

Duloxetine hydrochloride, hereafter referred to as duloxetine, is a selective 5-HT and NE reuptake inhibitor that is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition[12] and is the first Food and Drug Administration–approved prescription drug for the management of DPNP. In clinical trials, duloxetine has been shown to be safe and effective in the treatment of depression[13-15] and can significantly reduce painful physical symptoms associated with major depressive disorder (MDD).[16]

Based on preclinical[17] and clinical[16] studies of duloxetine, this compound was tested in an earlier study to explore its effects in humans with DPNP.[18] Patients with DPNP and without comorbid depression were randomly assigned to treatment with du-

loxetine 20 mg once daily (QD), 60 mg QD, or 60 mg twice daily (BID) or placebo for 12 weeks.[18] Based on evidence that duloxetine was safe and effective in the management of DPNP,[18] two independent confirmatory studies, the first of which is reported here, were conducted to assess the safety and efficacy of duloxetine in patients with DPNP. In the present study, patients with DPNP and without comorbid depression were randomly assigned to treatment with duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo for 12 weeks.

Methods. *Overview.* Enrollment for this study, which was conducted in 28 study centers, began in October 2002 and ended in August 2003. This was a Phase III, multicenter, parallel, double-blind, randomized, placebo-controlled trial. The ethical review board (ERB) provided approval of the study protocol in accordance with the principles of the Declaration of Helsinki. The ERB was composed of medical professionals and nonmedical members whose responsibility was to verify that the safety, welfare, and human rights of the patients participating in the clinical trial were protected. Investigators were responsible for monitoring the safety of patients who entered the study, and various safety measures were evaluated during the study. This study had no planned interim analysis. All patients provided written informed consent after the study was explained and before the performance of any protocol procedures and administration of the study drug.

Entry criteria. Female and male patients were eligible for the study if they were aged 18 years or older and presented with DPNP caused by type 1 or type 2 diabetes mellitus. The pain had to begin in the feet and with relatively symmetric onset. The daily pain must have been present for at least 6 months, and the diagnosis was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI). Patients had to have a mean score of ≥ 4 (between Visit 2 and Visit 3 before randomization), when assessed by 24-hour average pain severity on the 11-point Likert scale from the patient diary, a stable glycemic control assessed by a physician investigator, and a glycosylated hemoglobin (HbA$_{1c}$) $\leq 12\%$ (high HbA$_{1c}$ [$>9.0\%$ to 9.5%] is associated with rapid progression of microvascular complications). Only patients who were judged to be reliable and had an educational level and degree of understanding that allowed them to communicate intelligibly were included in the study. Patients were excluded if they were pregnant or breastfeeding, had previous renal transplant or current renal dialysis, or had a serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical conditions or psychological conditions that might compromise participation in the study. Patients were also excluded if they had a current (≤ 1 year) *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), Axis I diagnosis of MDD, dysthymia, generalized anxiety disorder, alcohol, or eating disorders as determined by the Mini International Neuropsychiatric Interview (MINI),[19] or if they had a previous diagnosis or a DSM-IV diagnosis of mania, bipolar disorder, or psychosis determined either by patient history or by diagnosis using specific MINI modules. Other exclusion criteria were historical exposure to drugs known to cause neuropathy, history of substance abuse or dependence within the previous year (excluding nicotine and caffeine), a positive urine drug screen for any substances of abuse or excluded medication, or a history of a medical condition, including pernicious anemia and hypothyroidism, or treatment with a monoamine oxidase inhibitor (MAOI) or fluoxetine within 30 days of randomization. Patients were excluded if they had severe allergic reactions to multiple medications and prior participation in a study of duloxetine.

Concomitant medication exclusions included chronic use of antidepressants, antiemetics, and analgesics with the exception of acetaminophen up to 4 g/day and aspirin up to 325 mg/day. Antimanics, antimigraines, antipsychotics, benzodiazepines, capsaicin, chloral hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psychostimulants, oral and injectable steroids, and anticonvulsants were excluded. Concomitant medication inclusions (chronic and episodic) were antacids, antiasthma agents, aminophylline,

birth control medication, cough/cold preparations (that did not contain dextromethorphan), diuretics, inhaled and topical steroids, hypoglycemics, insulin, laxatives, theophylline, anticoagulants, antibiotics, antidiarrheals, and antihistamines. Medications including angiotensin-converting enzyme inhibitors, angiotensin II receptor agonists, antiarrhythmics, anticoagulants, calcium channel blockers, and others were allowed provided the patient had been on a stable dose for 3 months before enrollment.

Patients were excluded if they had frequent or severe allergic reactions with multiple medications, had an alanine aminotransferase laboratory value > 1.5 times the upper limit of normal (ULN), and a serum creatinine laboratory value > 1.5 times ULN.

Study design. Visit 1 and Visit 2 occurred before randomization where entry criteria were evaluated for the patients. Those who continued to meet all inclusion criteria and no exclusion criteria proceeded to randomization at Visit 3. Randomization was performed at the site level in that randomization codes were assigned to sites in blocks, but there was no further stratification. After a 3-week assessment and screening period, patients with DPNP and without comorbid depression were randomly assigned to treatment with duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo in a 1:1:1 ratio. Assignment to a treatment group was determined by a computer-generated random sequence using an interactive voice response system (IVRS). The IVRS was used to assign blister cards containing study drug to each patient. Site personnel confirmed that they had located the correct blister card by entering a confirmation number found on the card into the IVRS. Throughout the course of the study, enrollment and patient progress was tracked using the IVRS. Patients were instructed to begin treatment the morning after randomization. The placebo-controlled, double-blind treatment phase lasted for 13 weeks. The first 12 weeks of the study period was considered the acute therapy phase, and the last week was used for drug tapering. The duloxetine 60 mg QD treatment group was started at 60 mg QD, and at the last week of the study period, the patients' dose was decreased to 30 mg QD. Patients who were randomized to duloxetine 60 mg BID were started initially at 60 mg QD for 3 days, and dosage was increased to 60 mg BID. At the last week of the study period, the patients' dose was decreased to 60 mg QD. Patients, investigators, and all other personnel involved with the conduct of the study were blinded to individual treatment assignments for the duration of the study.

Efficacy measures. The primary efficacy measure for this study was the reduction in weekly mean of the 24-hour average pain scores (computed from diary scores between two site visits), as measured by an 11-point (0 = no pain, 10 = worst possible pain) Likert scale that was completed daily by the patients in a diary. A reduction of approximately 2 points or approximately 30% in the 11-point pain intensity numerical rating scale represents a clinically important difference.[20] Protocol-specified response at endpoint was defined as a 30% reduction from baseline to endpoint in the 24-hour average pain score. Sustained response was defined as a 30% reduction from baseline to endpoint in the 24-hour average pain severity with a 30% reduction from baseline at a week at least 2 weeks before the last, and with at least a 20% reduction from baseline at every week in between. The amount of acetaminophen that was used to relieve pain over the past 24 hours was also recorded in the patients' diary. The secondary efficacy measures collected were pain severity for worst pain (referred to as 24-hour worst pain score hereafter) and night pain (recorded daily by patients in a diary) as measured by the 11-point Likert scale, the Patient's Global Impression of Improvement (PGI-Improvement) scale[21] recorded at weeks 4, 8, and 12, the Brief Pain Inventory (BPI) (severity),[22] and the Clinical Global Impression of Severity (CGI-Severity)[21] scales recorded at randomization, weeks 4, 8, and 12, and the Sensory Portion of the Short Form McGill Pain Questionnaire (SF-MPQ),[23] the 17-item Hamilton Depression Rating Scale (HAMD$_{17}$)[24,25] and dynamic allodynia that was recorded at randomization and week 12.

Health outcomes measures. The impact of duloxetine compared with placebo on patient-reported health outcomes was measured by the interference portion of the BPI, Short Form 36 (SF-36),[26] and European Quality of Life Instrument 5D version (EQ-5D).[27] The SF-36 was completed by the patient and measured how the patient perceived general status. The SF-36 consisted of 36 items that calculated eight health domains: bodily pain, general health, mental health, physical functioning, role–physical,
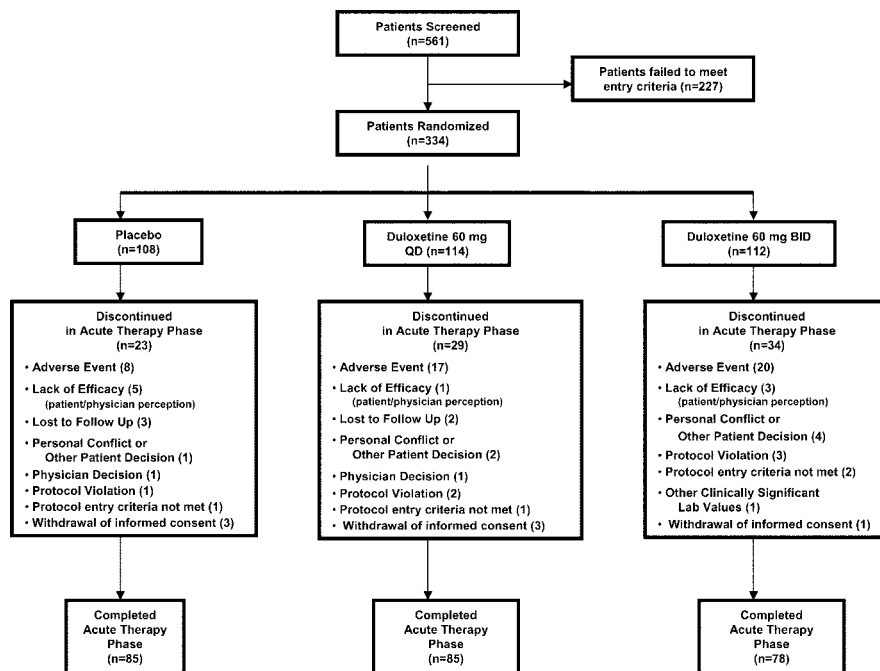
```
                    Patients Screened
                       (n=561)
                          │
                          ├──────────────→  Patients failed to meet
                          │                 entry criteria (n=227)
                    Patients Randomized
                       (n=334)
```

Figure 1. Flow diagram of patient progress through the trial. QD = once daily; BID = twice daily.

role–emotional, social function, and vitality. The EQ-5D was completed by the patient to measure how severe the patient perceived general health. The interference portion of the BPI was completed by the patient to measure how much pain had interfered with several patient outcomes, such as general activity, mood, walking ability, sleep, and relationships with other people.

Pharmacokinetic evaluation. Blood samples were collected for pharmacokinetic evaluation of plasma duloxetine concentrations at steady state.

Safety assessments. Safety measures evaluated during the study were discontinuations, treatment-emergent adverse events (TEAEs), vital signs (sitting blood pressure and heart rate), weight, electrocardiograms, and laboratory analyses. Electrophysiology assessment was performed using nerve conduction studies to determine whether duloxetine degraded motor and large sensory nerve (ulnar motor and sensory nerves, and peroneal motor nerve) function. The frequency of significant hypoglycemic events was elicited by a questionnaire derived from the results of the Diabetes Control and Complications Trial. A patient considered to have sustained elevation in blood pressure after randomization met the following criteria: sitting diastolic blood pressure ≥ 85 mm Hg and increase from baseline of 10 mm Hg for three consecutive visits, or sitting systolic blood pressure ≥ 130 mm Hg and increase from baseline of 10 mm Hg for three consecutive visits.

Statistical analysis. This study was designed to enroll 330 patients in 1:1:1 ratio to the three treatment groups (placebo, duloxetine 60 mg QD, and duloxetine 60 mg BID). With 110 patients per arm, this study would have at least 90% power to detect a treatment group difference of -1.20 points in the baseline-to-endpoint mean change on the weekly mean of 24-hour average pain score between duloxetine 60 mg BID and placebo treatment groups. The sample size was determined using a two-sided test with $\alpha = 0.05$ and assuming a common SD of 2.2 and a discontinuation rate of 35%.

An intent-to-treat principle was used in the analyses of all efficacy variables, i.e., patients were analyzed based on their randomized treatment assignment, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not follow or complete the protocol. For each efficacy variable, the analysis included all randomized patients with a baseline and at least one nonmissing postbaseline observation.

Baseline was defined as the last nonmissing observation at or before randomization, and endpoint was defined as the last nonmissing observation in the acute therapy phase. For the efficacy measures, the treatment group differences in change from baseline to endpoint were evaluated using the analysis of covariance (ANCOVA) model (with the terms of treatment, investigator, and the baseline). As specified in the protocol, the primary treatment

contrast was to compare duloxetine 60 mg BID with placebo using the Type III sum of squares for the least-square means, and thus, no adjustments for multiple pairwise comparisons were made. The treatment-by-investigator interaction was evaluated using the above model with the addition of the interaction term using the Type II sum of squares. Significant interaction was evaluated at the significance level of 0.10. The longitudinal observations on the efficacy variables were also analyzed using a repeated-measures analysis. The statistical inferences from the two different analytical methodologies demonstrated a high degree of consistency for all of the efficacy variables. Therefore, results from the ANCOVA were presented for the majority of the variables except for the primary efficacy measure, for which the results from both methodologies were presented. The weekly mean scores for the three pain scores (24-hour average pain, night pain, and 24-hour worst pain) were computed from patients' daily diaries. If the nonmissing diary count was <3, the mean score was set as missing.

Proportions were analyzed using the Fisher exact test. The average daily dose of acetaminophen used for DPNP relief was calculated from dosage collected from the patient's diary during the acute therapy and was analyzed using an analysis of variance (ANOVA) model on the rank-transformed data, because the distribution was skewed. The same approach was applied to the evaluation of weekly average number of significant hypoglycemic episodes.

Changes in vital signs, EKGs, and electrophysiology variables were evaluated using an ANOVA model with the terms of treatment, investigator, and treatment-by-investigator interaction, whereas laboratory analytes were evaluated in the rank-transformed format, because the distribution of raw data for most of the analytes was skewed.

Throughout the manuscript, the term *significant* indicates statistical significance, and when presenting efficacy results, the *mean change* refers to least-squares mean change.

Results. *Patient disposition, demographics, and disease characteristics.* The flow of patient progress through the trial is shown in figure 1. A total of 561 patients were screened to identify 334 patients who were randomized to study treatment. One-hundred eight patients received placebo, 114 patients received duloxetine 60 mg QD, and 112 patients received duloxetine 60 mg BID. Patient demographics and clinical characteristics at baseline are shown in table 1. The majority of patients were male (61.1%) and

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Table 1 *Demographics and clinical characteristics at baseline*

Variable	Placebo (n = 108)	Duloxetine 60 mg QD (n = 114)	Duloxetine 60 mg BID (n = 112)	Total (n = 334)
Mean age (SD), years	60.8 (10.6)	59.7 (11.2)	61.5 (9.9)	60.7 (10.6)
Sex, n (%)				
Female	39 (36.1)	40 (35.1)	51 (45.5)	130 (38.9)
Male	69 (63.9)	74 (64.9)	61 (54.5)	204 (61.1)
Race (origin), n (%)				
White	86 (79.6)	90 (78.9)	85 (75.9)	261 (78.1)
African descent	5 (4.6)	3 (2.6)	3 (2.7)	11 (3.3)
Hispanic	17 (15.7)	16 (14.0)	21 (18.8)	54 (16.2)
Other	0 (0.0)	5 (4.4)	3 (2.7)	8 (2.4)
Weight (SD), kg	104.4 (24.8)	99.9 (22.0)	98.7 (24.9)	101 (24.0)
Type of diabetes mellitus, n (%)				
Type I	11 (10.2)	10 (8.8)	9 (8.0)	30 (9.0)
Type II	97 (89.8)	104 (91.2)	103 (92.0)	304 (91.0)
Duration of diabetes (SD), years	11.1 (9.1)	9.7 (9.6)	9.9 (10.0)	10.2 (9.6)
Duration of diabetic neuropathy (SD), years	3.5 (3.2)	3.6 (3.5)	4.4 (5.9)	3.8 (4.4)
Michigan Neuropathy Screening Score, mean (SD)	5.9 (1.5)	5.5 (1.5)	5.6 (1.5)	5.6 (1.5)
Pain severity at baseline, mean (SD)				
24-Hour average pain severity	5.9 (1.4)	6.1 (1.6)	6.2 (1.5)	6.1 (1.5)
24-Hour worst pain severity	7.0 (1.5)	7.3 (1.7)	7.2 (1.6)	7.2 (1.6)
Night pain severity	6.2 (2.3)	6.3 (2.1)	6.2 (2.3)	6.3 (2.2)
BPI average interference score*	4.2 (2.2)	4.7 (2.5)	5.0 (2.4)	4.7 (2.4)
Total of SF-McGill	16.2 (7.5)	15.9 (7.7)	16.8 (6.7)	16.3 (7.3)
Dynamic allodynia	0.2 (0.5)	0.3 (0.6)	0.3 (0.7)	0.3 (0.6)
Mood and general illness, mean (SD)				
HAMD$_{17}$ total score	3.4 (2.7)	3.3 (3.4)	3.6 (3.0)	3.4 (3.1)
CGI-Severity	4.6 (0.8)	4.5 (0.9)	4.6 (0.8)	4.6 (0.8)

* $p < 0.05$.

QD = once daily; BID = twice daily; n = number of randomized patients; BPI = Brief Pain Inventory; SF = Short Form; HAMD$_{17}$ = 17-item Hamilton Rating Scale for Depression; CGI-Severity = Clinical Global Impression of Severity.

white (78.1%). The mean patient age was 60.7 years. The mean duration of diabetes in all patients was 10.2 years, with type II diabetes being the most prevalent (91%). The mean MNSI score was 5.6 out of a possible maximum score of 10, with a higher score indicating a greater degree of neuropathy.

Eighty-six patients withdrew from the study during the acute therapy phase: 29 (25%) from the duloxetine 60 mg QD-treated group, 34 (30%) from the duloxetine 60 mg BID-treated group, and 23 (21%) from the placebo-treated group (figure 1).

At baseline, a significant difference among treatment groups was observed for the BPI average interference score. The mean BPI average interference score was highest in the duloxetine 60 mg BID treatment group (5.0), followed by the duloxetine 60 mg QD treatment group (4.7) and the placebo treatment group (4.2).

Efficacy. The mean change from baseline to week 12 on the 24-hour average pain score is presented in table 2, and

the mean change from baseline to each postbaseline visit is shown in figure 2. Both duloxetine 60 mg QD and 60 mg BID were significant compared with placebo, thereby demonstrating a highly significant treatment effect of duloxetine on the management of DPNP as measured by the primary efficacy variable. A treatment-by-investigator interaction was observed ($p = 0.007$) on the 24-hour average pain score. The interaction was mainly caused by Investigator 004. The results from Investigator 004 showed that mean changes of 24-hour average pain scores for duloxetine 60 mg BID and placebo were opposite to the direction postulated: duloxetine 60 mg BID–treated patients got worse compared with baseline, whereas placebo-treated patients improved compared with baseline. The effect seen by Investigator 004 is qualitatively different from all other investigators. When Investigator 004 was excluded from the analysis, the treatment-by-investigator interaction was no longer significant, and both duloxetine 60 mg BID and duloxetine 60 mg QD remained significant compared with placebo ($p <$

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Table 2 *Mean change (SE) from baseline to endpoint: Efficacy measures*

	Placebo		Duloxetine 60 mg QD		Duloxetine 60 mg BID	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Weekly mean of						
24-Hour average pain score	106	−1.39 (0.23)	110	−2.72 (0.22)‡	111	−2.84 (0.23)‡
24-Hour worst pain score	106	−1.94 (0.25)	110	−3.21 (0.25)‡	111	−3.39 (0.26)‡
Night pain score	106	−1.83 (0.24)	109	−2.95 (0.25)†	111	−3.08 (0.25)‡
BPI pain severity						
Average pain	104	−1.48 (0.23)	112	−2.66 (0.23)‡	107	−3.05 (0.24)‡
Worst pain	104	−1.98 (0.28)	112	−3.33 (0.27)‡	107	−3.50 (0.28)‡
Least pain	104	−0.86 (0.22)	112	−1.88 (0.22)†	108	−2.30 (0.22)‡
Pain right now	104	−1.38 (0.23)	112	−2.48 (0.22)‡	108	−2.67 (0.23)‡
CGI-Severity	102	−0.98 (0.12)	111	−1.37 (0.11)*	106	−1.47 (0.12)†
PGI-Improvement (at endpoint)§	105	3.17 (1.44)	112	2.61 (1.44)†	107	2.40 (1.29)‡
SF-MPQ	91	−4.18 (0.73)	97	−7.23 (0.70)†	100	−7.98 (0.71)‡
HAMD$_{17}$	95	−0.64 (0.26)	97	−0.65 (0.26)	101	0.19 (0.26)*
Dynamic allodynia	98	−0.07 (0.04)	106	−0.11 (0.04)	102	−0.17 (0.04)

* $p < 0.05$ vs placebo.
† $p < 0.01$ vs placebo.
‡ $p < 0.001$ vs placebo.
§ For Patient's Global Impression of Improvement (PGI-Improvement), endpoint was analyzed and the mean (SD) is provided.

QD = once daily; BID = twice daily; n = number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable; BPI = Brief Pain Inventory; CGI-Severity = Clinical Global Impression of Severity; SF-MPQ = Short Form McGill Pain Questionnaire; HAMD$_{17}$ = 17-item Hamilton Rating Scale for Depression.

0.001). Therefore, with or without Investigator 004, the results demonstrated a highly significant treatment effect of duloxetine in the management of DPNP as seen on the primary efficacy variable. Duloxetine 60 mg QD and 60 mg BID treatment groups showed a significant decrease in pain severity compared with placebo beginning at week 1 and continuing throughout the study, with no significant difference between the duloxetine 60 mg QD and 60 mg BID treatment groups. The mean difference from placebo at endpoint was −1.32 (95% CI −1.95 to −0.69) for the duloxetine 60 mg QD treatment group and −1.44 (95% CI
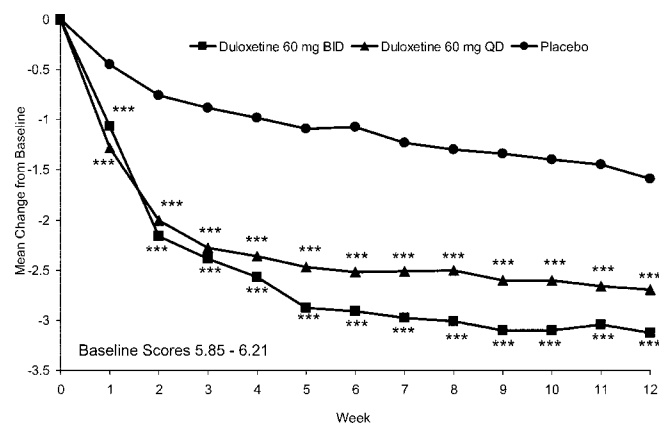

*Figure 2. Weekly mean change in 24-hour average pain severity score. *** $p < 0.001$ vs placebo. QD = once daily; BID = twice daily.*

−2.08 to −0.81) for the duloxetine 60 mg BID treatment group.

In the mean change analyses, duloxetine 60 mg QD and 60 mg BID were significant compared with placebo on all secondary measures (table 2) except for HAMD$_{17}$ total score and dynamic allodynia. Analyses of the 24-hour worst pain severity revealed that both duloxetine 60 mg QD and 60 mg BID were significant compared with placebo. Mean change analysis in night pain score showed that both duloxetine 60 mg QD and 60 mg BID were significant compared with placebo, beginning 1 week after randomization and continuing through the study. Both duloxetine 60 mg QD and 60 mg BID were significant compared with placebo on all BPI-Severity, CGI-Severity, and PGI-Improvement scale scores, as well as in improving the total score of the SF-MPQ.

A treatment-by-investigator interaction ($p < 0.10$) was observed for 24-hour worst pain severity, night pain severity, BPI individual severity score, and SF-MPQ total score. This interaction was no longer significant when Investigator 004 was excluded from the analyses, while the significance of the differences between duloxetine treatment group and placebo remained the same.

For the HAMD$_{17}$ total score, placebo was significant compared with duloxetine 60 mg BID. This finding, however, was likely due to noise of the data and was not clinically relevant because at baseline, due to exclusion criteria, patients demonstrated extremely low mean baseline HAMD$_{17}$ total scores (range of 3.31 to 3.55), as patients with depression were excluded from this study. Significant differences were observed
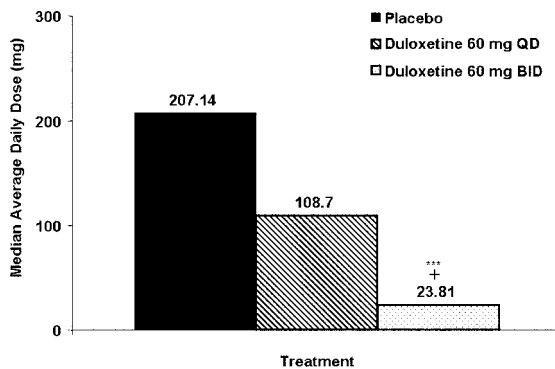
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Figure 3. Supplemental analgesic use for pain: median average daily dose of concomitant acetaminophen use. *** p < 0.001 vs placebo, + p < 0.05 vs duloxetine 60 mg QD, p value based on analysis of covariance for rank-transformed data. QD = once daily; BID = twice daily.

for both duloxetine 60 mg QD and 60 mg BID in the 24-hour average pain response rate at endpoint. A 30% reduction in the 24-hour average pain response, as specified by the protocol as the criterion for response, was achieved by 42% of

patients in the placebo-treated group, 63% in the duloxetine 60 mg QD–treated group ($p = 0.003$ vs placebo), and 69% in the duloxetine 60 mg BID–treated group ($p < 0.001$ vs placebo). A 50% reduction in the 24-hour average pain response was achieved by 27% of patients in the placebo-treated group, 43% in the duloxetine 60 mg QD–treated group ($p < 0.05$ vs placebo), and 53% in the duloxetine 60 mg BID–treated group ($p < 0.001$ vs placebo). Duloxetine 60 mg QD ($p = 0.004$) and 60 mg BID ($p < 0.001$) demonstrated significance compared with placebo at achieving sustained response. Sustained response was achieved by 54% of duloxetine 60 mg QD– and 62% of duloxetine 60 mg BID–treated patients compared with 34% of placebo-treated patients.

Concomitant acetaminophen use during the acute therapy phase. The median average daily dose for concomitant acetaminophen used for DPNP collected from the patient diary during the acute therapy phase indicated that patients treated with duloxetine 60 mg BID used a significantly lower median daily dose of concomitant acetaminophen compared with patients treated with duloxetine 60 mg QD or placebo-treated patients (figure 3).

Table 3 *Mean change (SE) from baseline to endpoint: Health outcome measures*

| | Placebo | | Duloxetine | | | |
| | | | 60 mg QD | | 60 mg BID | |
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
SF-36						
Physical functioning	101	3.64 (1.90)	109	11.96 (1.81)†	108	11.20 (1.86)†
Social functioning	101	3.68 (2.14)	109	7.50 (2.06)	108	7.61 (2.09)
Role–physical	101	12.14 (3.77)	109	22.85 (3.63)*	108	25.01 (3.67)*
Role–emotional	100	2.13 (3.44)	108	10.66 (3.32)	108	9.00 (3.35)
Bodily pain	101	12.17 (2.10)	109	15.30 (1.98)	107	20.59 (2.04)†
General health	101	2.39 (1.42)	108	5.64 (1.38)	107	7.73 (1.39)†
Vitality	101	2.79 (1.78)	108	8.47 (1.73)*	108	6.36 (1.74)
Mental health	101	−0.31 (1.52)	108	1.63 (1.48)	108	3.82 (1.49)*
Physical component score	100	3.67 (0.78)	107	6.85 (0.76)†	106	7.46 (0.77)‡
Mental component score	100	−0.29 (0.83)	107	0.77 (0.81)	106	1.09 (0.82)
Euro Quality of Life (EQ-5D)	99	0.08 (0.02)	108	0.15 (0.02)*	105	0.15 (0.02)*
BPI Interference						
General activity	104	−1.79 (0.23)	111	−2.40 (0.23)	107	−2.57 (0.23)*
Mood	104	−1.37 (0.21)	111	−1.95 (0.21)*	107	−2.48 (0.21)‡
Walking ability	104	−1.74 (0.25)	111	−2.50 (0.24)*	107	−2.96 (0.25)‡
Normal work	104	−2.03 (0.24)	111	−2.49 (0.23)	107	−2.93 (0.24)†
Relationship with other people	104	−0.88 (0.19)	111	−1.44 (0.18)*	107	−1.81 (0.19)‡
Sleep	104	−2.34 (0.26)	111	−3.02 (0.26)	107	−3.17 (0.26)*
Enjoyment of life	104	−2.24 (0.23)	111	−2.58 (0.23)	107	−3.42 (0.23)‡
Average of interference scores	104	−1.72 (0.19)	111	−2.36 (0.19)*	107	−2.79 (0.19)‡

* $p < 0.05$ vs placebo.

† $p < 0.01$ vs placebo.

‡ $p < 0.001$ vs placebo (pairwise comparison of least square means).

QD = once daily; BID = twice daily; n = number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable; SF-36 = Short Form 36; EQ-5D = European Quality of Life Instrument 5D version; BPI = Brief Pain Inventory.

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Table 4 *Top 10 treatment-emergent adverse events of all randomized patients, by decreasing frequency*

	Placebo (n = 108), n (%)	Duloxetine 60 mg QD (n = 114), n (%)	Duloxetine 60 mg BID (n = 112), n (%)	Total (n = 334), n (%)
Nausea	7 (6.5)	32 (28.1)‡	36 (32.1)‡	75 (22.5)
Dizziness	6 (5.6)	18 (15.8)*	12 (10.7)	36 (10.8)
Headache	7 (6.5)	12 (10.5)	15 (13.4)	34 (10.2)
Constipation	2 (1.9)	8 (7.0)	21 (18.8)‡	31 (9.3)
Fatigue	3 (2.8)	14 (12.3)*	14 (12.5)*	31 (9.3)
Somnolence	1 (0.9)	9 (7.9)*	17 (15.2)‡	27 (8.1)
Diarrhea	2 (1.9)	13 (11.4)†	5 (4.5)	20 (6.0)
Nasopharyngitis	5 (4.6)	8 (7.0)	7 (6.3)	20 (6.0)
Insomnia	2 (1.9)	6 (5.3)	11 (9.8)*	19 (5.7)
Sweating increased	1 (0.9)	10 (8.8)*	8 (7.1)*	19 (5.7)

* $p < 0.05$ vs placebo.

† $p < 0.01$ vs placebo.

‡ $p < 0.001$ vs placebo (Fisher exact p values).

QD = once daily; BID = twice daily; n = number of randomized patients.

Health outcomes analyses. In the SF-36 health survey, duloxetine 60 mg QD was significantly better than placebo in the physical component summary and the domains of physical functioning, role limitations due to physical problems, and vitality (table 3). Duloxetine 60 mg BID was significantly better than placebo in the physical component summary and domains of bodily pain, general health perceptions, mental health, physical functioning, and role limitations due to physical problems. In the analysis of the EQ-5D, duloxetine 60 mg QD and 60 mg BID were both significantly better than placebo. Duloxetine 60 mg BID was significant compared with placebo at reducing scores in all BPI interference scales.

A significant treatment-by-investigator interaction was observed for physical functioning and bodily pain on the SF-36 and the EQ-5D index score. The interaction was no longer significant when Investigator 004 was excluded, and the results of statistical comparison remained the same.

Pharmacokinetic evaluation. Plasma duloxetine concentrations in patients taking duloxetine 60 mg BID were 96.6 (SD = 83.3) ng/mL, and those in patients taking duloxetine 60 mg QD were 41.3 (SD = 37.4) ng/mL.

Safety. Adverse events. Of the 334 randomly assigned patients, 79 placebo-treated patients (73.1%), 102 duloxetine 60 mg QD–treated patients (89.5%) ($p = 0.002$ vs placebo), and 96 duloxetine 60 mg BID–treated patients (85.7%) ($p = 0.029$ vs placebo) reported at least one TEAE. Table 4 shows the top 10 TEAEs by decreasing frequency. Patients in both duloxetine-treated groups reported treatment-emergent nausea, fatigue, somnolence, increased sweating, and dry mouth significantly more frequently than placebo-treated patients. Additionally, compared with placebo-treated patients, dizziness and diarrhea were reported significantly more frequently by duloxetine 60 mg QD–treated patients, and constipation, insomnia, decreased appetite, asthenia, erectile dysfunction, and tremor were reported significantly more frequently by duloxetine 60 mg BID–treated patients. Forty-five patients (13.5%) dis-

continued during the therapy phase because of adverse events (duloxetine 60 mg QD, 17 [14.9%]; duloxetine 60 mg BID, 20 [17.9%]; placebo, 8 [7.4%]), with differences between duloxetine 60 mg BID– and placebo-treated groups ($p = 0.025$). Nausea (5.3%) and dizziness (2.6%) were reported as reasons for discontinuation in >1% of duloxetine 60 mg QD–treated patients. Nausea (5.4%), fatigue (2.7%), and somnolence (2.7%) were reported as reasons for discontinuation in >1% of duloxetine 60 mg BID–treated patients.

A serious adverse event was defined as any adverse event from the study resulting in one of the following outcomes (or was significant for any other reason): death, initial or prolonged inpatient hospitalization, a life-threatening experience, persistent or significant disability/incapacity, or congenital anomaly/birth defect. No deaths were reported during the study. Twelve patients (3.6%) experienced serious adverse events with no significant treatment group differences. These included 5 duloxetine 60 mg QD–treated patients (4.4%) (events: congestive cardiac failure, coronary artery stenosis, hip fracture, prostate cancer, hypokalemia, hyponatremia), 2 duloxetine 60 mg BID–treated patients (1.8%) (events: blood calcium increased, concussion), and 5 placebo-treated patients (4.6%) (events: atrioventricular block second degree, carcinoma, chronic obstructive airways disease exacerbated, diabetic ulcer, fatigue, hypertension).

Twenty-eight (8.4%) of the 334 patients reported at least one adverse event that emerged during the 1-week drug taper phase (7 duloxetine 60 mg QD–treated patients [6.1%], 10 duloxetine 60 mg BID–treated patients [8.9%], and 11 placebo-treated patients [10.2%]; no events occurred in ≥1% of patients in either duloxetine treatment group, and in the placebo-treated group, the events reported by ≥1% of patients were headache [2.8%] and arthralgia [1.9%]). There were no significant treatment group differences in the overall incidence of taper-emergent adverse events or in any single taper-emergent adverse event.

Table 5 *HbA$_{1c}$ and lipid profile: Mean change from baseline to endpoint*

| | Placebo (n = 82–101) | Duloxetine | |
		60 mg QD (n = 88–105)	60 mg BID (n = 95–108)
HbA$_{1c}$, %	−0.0005	−0.0018	−0.0004
p Value		0.967	0.259
LDL-cholesterol, mmol/L	0.017	0.023	0.113
p Value		0.689	0.177
HDL-DX, mmol/L	0.002	0.033	0.062
p Value		0.183	0.009
Triglycerides, mmol/L	0.265	−0.136	−0.394
p Value		0.169	0.070

p values vs placebo (least-squares mean option, using mean squares for error).

QD = once daily; BID = twice daily; n = total number of patients in each treatment group having the variable in both baseline and postbaseline visits; HbA$_{1c}$ = glycosylated hemoglobin; LDL-C = low-density lipoprotein cholesterol; HDL-DX = high-density lipoprotein cholesterol-dextran precip.

Laboratory data, vital signs, and electrocardiographic data. Although duloxetine-treated patients showed changes in chemistry laboratory assessments, these changes were of low magnitude and not considered clinically relevant. Duloxetine 60 mg QD– and 60 mg BID–treated patients experienced a significant mean increase in alkaline phosphatase (ALKPH) compared with placebo-treated patients. Duloxetine 60 mg BID–treated patients experienced a significant mean decrease in chloride and uric acid and duloxetine 60 mg QD–treated patients experienced a significant mean increase in inorganic phosphorous compared with placebo-treated patients. Bilirubin was elevated in association with elevation of aspartate transaminase/serum glutamic oxaloacetic transaminase in one duloxetine 60 mg QD–treated patient and with elevation of creatine phosphokinase (CPK) in one placebo-treated patient. In this 12-week study, duloxetine did not seem to adversely affect lipid profiles (table 5) or glycemic control (table 6).

There were no significant mean changes in ulnar and peroneal nerve function measures from baseline to endpoint in patients receiving duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo. Duloxetine did not prolong the QT interval. There were no significant treatment group differences in mean change of systolic and diastolic blood pressure. Patients treated with duloxetine 60 mg BID experienced a slight but significant mean increase in

heart rate (2.41 beats per minute [bpm]) compared with duloxetine 60 mg QD–treated patients (−0.35 bpm) and placebo-treated patients (−0.99 bpm), and patients in both duloxetine-treated groups experienced a slight but significant mean decrease in weight (−1.37 kg in each group) compared with placebo-treated patients (−0.01 kg). However, neither of these effects was considered clinically relevant.

Discussion. Diabetes mellitus is common in the United States, and it is estimated that the prevalence of neuropathy in diabetic patients is 30% in hospital patients and 20% in community patients.[28] Over time, neuropathic pain can become a common complication. The first line of management of DPNP has involved administration of TCAs with reuptake inhibitory activity for both 5-HT and NE and anticonvulsants.[4,6,29,30] However, because this condition primarily affects the elderly, these patients may be more susceptible to the α-adrenergic blocking, anticholinergic, and cardiac conduction effects associated with TCAs. Other treatments have involved capsaicin cream and isosorbide dinitrate spray.

Although head-to-head comparison studies have not been conducted, a great deal of evidence suggests that dual 5-HT and NE reuptake inhibitors provide better efficacy, whereas randomized trials of selective serotonin reuptake inhibitors (SSRIs) overall have shown minimal efficacy of SSRIs in relieving DPNP.[31-33] Treatment with the 5-HT and NE reuptake inhibitor venlafaxine at high doses resulted in lower pain intensity and greater pain relief.[34] Various other studies have shown that venlafaxine may be useful in treating pain associated with diabetic neuropathy.[35-37] However, at low doses, it is predominantly serotonergic, whereas higher doses add substantial noradrenergic effects.[36] Duloxetine has a higher affinity for both 5-HT and NE transporters[38] and is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition.[12] It is effective in treating pain in animal models.[17,39] It is also effective

Table 6 *Weekly average number of significant hypoglycemic episodes*

| | Placebo (n = 106) | Duloxetine | |
		60 mg QD (n = 112)	60 mg BID (n = 111)
Mean	0.08	0.06	0.12
SD	0.39	0.19	0.43
Median	0.00	0.00	0.00
p Value vs placebo (rank-transformed data)	—	0.198	0.109

QD = once daily; BID = twice daily.

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in reducing the severity of painful physical symptoms associated with depression in patients with MDD.[16,40] Because noradrenergic and serotonergic neurons may modulate the endogenous pain inhibitory pathways,[9,10] the ability of duloxetine to exert its effects on both these neurotransmitter systems may explain its effectiveness in this clinical trial.

This study confirms previous findings that duloxetine at 60 mg QD and 60 mg BID was safe and demonstrated robust evidence of efficacy in the management of DPNP.[18] Both studies were adequately designed and powered a priori to ensure that a statistical comparison of efficacy between placebo- and duloxetine-treated groups could be undertaken. In both studies, beginning in week 1, duloxetine was significant compared with placebo in improvement of a priori–declared primary outcome measure, the 24-hour average pain score. An earlier study conducted[18] also included a dose of duloxetine 20 mg to establish a subtherapeutic dose in the management of DPNP. The 20 mg QD dose of duloxetine did not show significant separation from placebo on the primary efficacy measure and many secondary efficacy measures. Effect size presentation for 24-hour average pain score, response rate, and sustained response rate clearly and consistently demonstrated that duloxetine 60 mg QD was more efficacious than duloxetine 20 mg QD. In the study presented here, significant pain reduction was demonstrated on the 24-hour average pain score, worst pain score, night pain score, and various health outcome measures. This demonstrates the clinical relevance of the changes in pain severity observed.

Although the $HAMD_{17}$ rating scale showed that placebo was significant compared with duloxetine 60 mg BID, this difference was not clinically relevant because patients had low mean baseline $HAMD_{17}$ scores (3.4) due to exclusion criteria. A $HAMD_{17}$ score of ≤ 7 is often used as an indicator of remission in the MDD population. These patients were normal with regard to mood disorder; thus there was minimal room for improvement in mood.

The incidence of serious adverse events was low, and no deaths occurred during the study. The only adverse events leading to discontinuation in $\geq 1\%$ of duloxetine-treated patients were nausea, dizziness, somnolence, and fatigue. Although nausea was the most frequently reported adverse event, it usually occurred at the beginning of treatment and decreased quickly over time. Patients in the present study were started on duloxetine 60 mg QD and underwent titration to 60 mg BID over just 3 days. Results from a previous study in patients with MDD suggest that initiating duloxetine treatment at 30 mg QD for 1 week, followed by escalation to 60 mg QD, may reduce the risk of treatment-emergent nausea when compared with starting at 60 mg QD.[41] These results suggest that some patients would have better tolerability with a lower duloxetine starting dose and slower titration. In this study, no adverse effects on glycemic control or lipid profiles were detected. Duloxetine did not prolong the QT interval or cause a significant change in blood pressure compared with placebo. There were no clinically relevant changes in heart rate or weight that were experienced by patients taking duloxetine 60 mg QD or 60 mg BID in this trial. The lack of significant treatment-group differences in any of the electrophysiology measures indicated that duloxetine did not alter motor and large sensory nerve fiber function in DPNP patients. The safety findings reported in this study are in general agreement with the findings in other studies that indicate that duloxetine-treated patients with depression do not experience clinically relevant changes in heart rate and blood pressure.[13,15] In summary, duloxetine was generally well tolerated, although it is not without side effects.

The efficacy of duloxetine 60 mg QD and that of duloxetine 60 mg BID were similar, and the numeric advantage of the higher dose on many outcome measures was not significant. Previous studies have shown that duloxetine exhibits linear pharmacokinetics with regard to dose and duration of treatment,[42] and the results of the trial presented here show that plasma concentrations in patients taking duloxetine 60 mg BID were slightly more than twice those in patients taking duloxetine 60 mg QD. Because duloxetine 60 mg QD represents the lowest consistently effective total daily dose and considering the advantage of a once-daily regimen and administration of a lower total daily dose, the recommended dose of duloxetine in the management of DPNP is 60 mg QD. Although a higher dose may be less well tolerated, some patients may obtain an additional benefit from doses up to 60 mg BID.

Appendix

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ORIGINAL ARTICLE

A Randomized, Controlled Trial of Gabapentin Enacarbil in Subjects with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

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■ **Abstract**

Background: Gabapentin enacarbil (GEn), a transported prodrug of gabapentin, provides sustained, dose-proportional gabapentin exposure. The purpose of this study was to investigate the dose response of GEn to select the optimal dose(s) for clinical use in subsequent diabetic peripheral neuropathy (DPN) trials.

Methods: This was a multicenter, randomized, double-blind, double-dummy, parallel group, placebo-controlled trial with a study duration of approximately 20 weeks (Clinicaltrials.gov database, Identifier # NCT00643760). Pregabalin (PGB) (Lyrica®; Pfizer Inc.) was used as an active control to provide assay sensitivity of the trial. A total of 421 adult subjects with DPN were randomized in a ratio of 2:1:1:1:2 to receive oral GEn 3,600 mg/day, GEn 2,400 mg/day, GEn 1,200 mg/day, PGB 300 mg/day, or matching placebo, respectively. The primary efficacy endpoint was change from baseline to end of maintenance treatment with respect to the mean 24-hour average pain intensity score based on an 11-point Pain Intensity Numerical Rating Scale (PI-NRS). Safety and tolerability assessments included treatment-emergent adverse events (TEAEs), laboratory evaluations, vital signs, electrocardiograms (ECG), neurological examination, and pedal edema.

Results: The adjusted mean difference vs. placebo at the end of maintenance treatment with respect to the mean 24-hour average PI-NRS pain intensity score for GEn 1,200 mg (−0.35; [95% CI: −1.02, 0.31]; P = 0.295), GEn 2,400 mg (−0.02; [95% CI: −0.71, 0.66]; P = 0.946), and GEn 3,600 mg (−0.55; [95% CI: −1.10, 0.01]; P = 0.105) was not statistically significant. The active control, PGB (300 mg/day), did not differentiate from placebo.

Conclusion: Overall, none of the GEn treatment groups differentiated from placebo. Analyses of the secondary endpoints showed comparable results across treatment groups. However, the majority of the endpoints, including all of the pain endpoints, showed the largest numerical treatment difference was between GEn 3,600 mg and

placebo. The active control, PGB (300 mg/day), did not differentiate from placebo. ■

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes, is a common condition in the developed world and its prevalence is increasing rapidly. Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus and can occur in 34–90% of the diabetic population, depending on the diagnostic criteria used[1–6]. While not all DPN is painful, pain can develop as a symptom of DPN. It is estimated that between 16% and 26% of diabetic subjects experience chronic neuropathic pain associated with DPN[7].

Neuropathic pain associated with DPN is caused by lesions or dysfunction of the peripheral and/or central nervous system and does not require receptor stimulation. Painful sensations are most commonly relayed via small primary afferents, the A-δ fibers, and unmyelinated C fibers to the dorsal horn of the spinal cord where a synaptic junction in the outer part of the dorsal horn subsequently relays sensations to the spino-parabrachial-amygdaloid pathway and spinothalamic tract[7]. Neuropathic pain is a paradox, in that there is development of pain in the area where the subject experiences sensory deficit due to nerve injury. Neuropathic pain results from plastic changes in the nervous system of some, although not all, subjects that leads to increased excitability of the remaining and surrounding neurons and results in the experience of pain.

Since 1999, the United States (US) Food and Drug Administration (FDA) has approved two medications for the management of neuropathic pain associated with DPN: pregabalin (Lyrica®; Pfizer Inc., New York, NY, USA) and duloxetine (Cymbalta®; Eli Lilly & Co., Indianapolis, IN, USA). Other nonapproved pharmacotherapies commonly used for treatment include gabapentin, tricyclic antidepressants, and opioids. In clinical trials, pregabalin and duloxetine have both been shown to improve pain scores in DPN subjects. However, less than half of subjects in the clinical trials with pregabalin and duloxetine experienced at least 50% reduction in pain score from baseline[8,9]. Both the degree and variability of effectiveness of the currently approved medicines suggests that there are patients with neuropathic pain associated with DPN who might benefit from a new treatment option.

Gabapentin enacarbil (GEn [XP13512/GSK1838262]) is a prodrug of gabapentin designed to overcome the pharmacokinetic limitations of gabapentin. Unlike orally administered gabapentin, which is absorbed by low capacity transporters expressed in a limited region of the upper intestine, GEn is designed to be absorbed by high-capacity transport mechanisms located throughout the intestinal tract, including the colon[10]. GEn is well absorbed and provides rapid and extended delivery of gabapentin into the systemic circulation, offering predictable absorption, dose-proportional gabapentin exposure, and the opportunity to optimize gabapentin exposure to patients. Additionally, GEn has been formulated as an extended release (ER) formulation, thereby providing less frequent dosing compared with gabapentin.

The current study, PXN110448, explored the efficacy of GEn in the treatment for neuropathic pain associated with DPN. Study medication included different doses of GEn, pregabalin (PGB), and placebo.

METHODS

This study (PXN110448, Clinicaltrials.gov Identifier # NCT00643760) was conducted at 85 centres in the US, from March 2008–February 2009, in accordance with "good clinical practice" (GCP) and all applicable subject privacy requirements, the guiding principles of 21 Code of Federal Regulations parts 312, 50, and 56, and of the Declaration of Helsinki. The study protocol, the informed consent, and other information that required preapproval were reviewed and approved by applicable institutional review boards or ethics committees. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.

Study Population

Men and women at least 18 years of age who were diagnosed with diabetes mellitus (type 1 or 2) and had pain attributed to DPN, defined as painful distal symmetric sensorimotor polyneuropathy, for at least 6 months and no greater than 5 years were considered for inclusion. Subjects must have had pain attributed to their DPN of at least moderate intensity, defined as an average pain intensity score of ≥ 4 on an 11-point pain intensity numerical rating scale (PI-NRS) where 0 = no pain and 10 = worst possible pain. During the 7 days

preceding randomization, subjects recorded pain scores at least 4 of 7 days in a daily pain diary.

Enrolled subjects were required to have stable glycemic control 3 months prior to randomization and glycosylated hemoglobin (HbA1c) levels < 8% at the time of randomization (levels were permitted to range between 8–11% if attempts to control diabetes had failed). Women of childbearing potential were required to have a negative pregnancy test and were willing to use an effective method of contraception throughout the study. Acetaminophen, up to 3 g/day, was allowed as rescue medication for pain throughout the trial but was not allowed within 24 hours of any site visit for assessments.

Key exclusion criteria included the following:

- Subjects with chronic pain due to neuropathy or lower extremity pain not related to DPN. However, subjects with chronic pain conditions not associated with DPN were not excluded if the pain was located at a different region of the body, the pain intensity was not greater than the pain intensity of the DPN pain, and the subject was able to assess DPN pain independently of other pain conditions.
- Subjects with conditions (eg unstable depression, alcohol, substance abuse) or medications (eg acute pain medications, hypnotics, antidepressants) that could possibly have interfered with the assessment of pain improvement following the use of Gen.
- Subjects with pre-existing liver, renal, cardiovascular, disease, epilepsy or seizure disorders, or any other medical condition or treatment that could have interfered with the accurate assessment of the efficacy, safety, or absorption of Gen.
- Subjects who were currently participating in other clinical trials or who had been recently exposed to, or had an allergic reaction to, GEn or its components or acetaminophen or compounds closely related to acetaminophen.

Study Design

This was a multicenter, randomized, double-blind, double-dummy, parallel group, placebo-controlled, and active-controlled study to investigate the dose response of GEn in subjects with neuropathic pain associated with DPN.

The duration of the study was approximately 20 weeks, divided into six phases: screening (up to 4 weeks); baseline (including randomization, 1 week); up-titration (1 week); maintenance phase (dose maintained at fixed level, 12 weeks); down-titration (1 week); and follow-up phase (1 week after last investigational product dose; 16 days for females of child bearing potential).

Subjects were randomized to receive GEn 3,600 mg/day, GEn 2,400 mg/day, GEn 1,200 mg/day, PGB 300 mg/day, or matching placebo in a 2:1:1:1:2 randomization ratio according to a computer-generated schedule. Gabapentin enacarbil was provided as 600 mg tablets with identical-in-appearance placebo tablets to ensure blinding of subjects and investigators; PGB was provided as 50 mg and 100 mg with identical-in-appearance placebo capsules and was administered in accordance with the recommended dose for the management of neuropathic pain associated with DPN specified in the FDA approved package label[8]. To maintain blinding during the maintenance phase, all subjects were instructed to take the study medication as indicated in Table 1 in the morning, afternoon, and evening. All GEn and matching placebo tablets were provided in Medisets that were filled by an unblinded, third-party pharmacist; all PGB and matching placebo capsules were provided in blister cards.

Table 1. Treatment Cohorts

Cohort	Randomization Ratio (n = Planned Number of Randomized Subjects)	Maintenance Treatment Total Daily Regimen
Placebo (PBO)	2 (n = 112)	GEn PBO X 6 (3 tablets twice daily); PGB PBO X 3 (1 capsule 3 times daily)
GEn 1,200 mg/day	1 (n = 56)	GEn 600 mg X 2 (1 tablet twice daily); GEn PBO X 4 (2 tablets twice daily); PGB PBO X 3 (1 capsule 3 times daily)
GEn 2,400 mg/day	1 (n = 56)	GEn 600 mg X 4 (2 tablets twice daily); GEn PBO X 2 (1 tablet twice daily); PGB PBO X 3 (1 capsule 3 times daily)
GEn 3,600 mg/day	2 (n = 112)	GEn 600 mg X 6 (3 tablet twice daily); PGB PBO X 3 (1 capsule 3 times daily)
PGB 300 mg/day	1 (n = 56)	PGB 100 mg X 3 (1 capsule 3 times daily); GEn PBO X 6 (3 tablets twice daily)

Study Assessments

The primary objective of the study was to investigate the dose response of GEn using improvement in pain intensity scores to select the optimal dose(s) for clinical use in subsequent DPN trials.

Additional (secondary) objectives included characterizing the effect of GEn on improvement in pain parameters, physical and emotional function, and global improvement; investigating the safety of GEn; and estimating the systemic exposure of gabapentin associated with GEn doses of 1,200 mg/day, 2,400 mg/day, and 3,600 mg/day.

The primary efficacy assessment instrument was the 11-point PI-NRS as completed by subjects in their daily pain diary. Subjects described their pain during the previous 24 hours by choosing the appropriate number from 0 ("no pain") to 10 ("pain as bad as you can imagine"). The primary analysis compared the change from baseline to end of maintenance treatment (EOMT) with respect to the mean 24-hour average pain intensity score. The baseline score was the calculated mean of the daily 24-hour average pain scores for each subject during the last 7 days prior to randomization. The EOMT score was the calculated mean of the daily 24-hour average pain scores for each subject during the last seven days of the maintenance phase.

The secondary efficacy endpoints included the change from baseline in the mean: 24-hour average pain intensity score, daytime average pain intensity score, nighttime average pain intensity score, current pain intensity score, daytime worst pain intensity score, nighttime worst pain intensity score, sleep interference score, and rescue analgesia consumption (mg), each of which was analyzed at each week of treatment and post-treatment.

Other efficacy endpoints included: the Neuropathic Pain Scale (NPS); Short-Form McGill Pain Questionnaire (SF-MPQ); pre- and post-50-foot (15 meter) walk pain scores; proportion of subjects who were "much improved" or "very much improved" on the Patient Global Impression of Change (PGIC) and Clinician Global Impression of Change (CGIC) questionnaires; proportion of subjects achieving various levels of reduction in the 24-hour average pain intensity score; time to onset of sustained improvement in the 24-hour average pain intensity score; Profile of Mood State (POMS); and Short-Form-36 (SF-36) health-related quality of life questionnaire.

The safety assessments included treatment-emergent adverse events (TEAEs), possible suicidality-related adverse events (PSRAEs), laboratory evaluations (blood chemistry, hematology, immunology, urinalysis, pregnancy), vital signs (blood pressure, heart rate), electrocardiograms (ECG), and a neurological exam, including a detailed examination of sensory and motor systems, body weight, and pedal edema. The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an AE or a serious adverse event (SAE) as defined in the study protocol; adverse events were collected at each study visit.

The objective of the population PK analysis was to derive the daily area under the gabapentin plasma concentration curve (AUC_{0-24}) in each subject with neuropathic pain associated with DPN. A Bayesian approach was applied to estimate individual PK parameters assuming the population PK model previously estimated with data from healthy subjects and subjects with RLS as priors. A population PK/PD model, describing the relationship between gabapentin systemic exposure and pain intensity scores, was then developed. In addition, the potential effects of covariates (age, body weight, height, body mass index, sex, concomitant medications, and baseline pain score) on the defined exposure–response relationship were investigated.

Statistical Methods

The study was originally designed to assess dose response from an anticipated Emax distribution. Consequently, there was an unequal randomization to the different treatment arms. However, the primary statistical analysis (per-protocol amendment 3) was designed to test each potential dose (GEn 3,600 mg/day, GEn 2,400 mg/day, or GEn 1,200 mg/day) against placebo. A planned sample size of 336 subjects, randomized in a 2:1:1:2 ratio (GEn 3,600 mg/day:GEn 2,400 mg/day: GEn 1,200 mg/day:Placebo) (112:56:56:112), provided power ranging between 71 and 96% to detect a treatment effect of 1.2 points in mean pain intensity score as compared to placebo, assuming a standard deviation of 2.45. Additionally, 56 subjects were to be randomized to PGB (300 mg/day) as an active control to provide a descriptive assessment of the assay sensitivity of the study. To protect the experiment-wise alpha level of 0.05, a combination of sequential methods and a Hochberg procedure was used for the primary endpoint.

Based on a simulation of the Hochberg method for adjusting for multiple comparisons, if both GEn 3,600 mg/day and GEn 2,400 mg/day were effective, there would be approximately 96% power to detect a difference for at least one of the comparisons, GEn 3,600 mg/day vs. placebo and GEn 2,400 mg/day vs. placebo. If only GEn 3,600 mg/day was effective, there would be 88% power to detect a difference between GEn 3,600 mg/day and placebo at an alpha level of 0.025. If only GEn 2,400 mg/day was effective, there would be 71% power to detect a difference between GEn 2,400 mg/day and placebo at an alpha level of 0.025.

The GEn 1,200 mg/day dose was to be compared with placebo only if both of the higher doses were statistically significant at an alpha level of 0.05. Formal statistical testing of PGB to placebo was not conducted.

The Safety Population, used to assess safety endpoints, was composed of all subjects who took at least one dose of investigational product. The Intent-to-Treat (ITT) Population, used to assess all efficacy endpoints, comprised all randomized subjects who took at least one dose of investigational product and provided at least one postbaseline efficacy measurement. The Per-Protocol (PP) Population was defined as all subjects in the ITT Population who had no major protocol deviations. The PK Population was defined as all randomized subjects who took at least one dose of investigational product and provided at least one PK sample.

The primary efficacy analysis used the last observation carried forward (LOCF) approach for imputation of data for subjects who did not complete the study. Sensitivity analyses using baseline observation carried forward (BOCF), BOCF/LOCF Hybrid and observed cases (OC) data for noncompleters, were also performed. Finally, a mixed-model repeated measures (MMRM) analysis was performed as an additional sensitivity analysis for the primary efficacy variable using the OC data for the ITT population.

For endpoints assessed as a change from baseline, including the primary efficacy endpoint, each dose of GEn was compared with placebo using an Analysis of Covariance (ANCOVA) model, with body mass index (BMI), baseline score for the endpoint being analyzed, grouped centre, and randomized treatment as terms in the model. The proportion endpoints (eg proportion of subjects who are "much improved" or "very much improved" per the PGIC and CGIC) were analyzed using logistic regression with grouped centre and randomized treatment as terms in the model (PGIC), or

with randomized treatment as the only term in the model (CGIC).

RESULTS

Subject Disposition and Baseline Characteristics

There were 421 subjects randomized in a 2:1:1:1:2 ratio (GEn 3,600 mg/day:GEn 2,400 mg/day:GEn 1,200 mg/day:PGB 300 mg/day:Placebo) in the study (*n* = 117 GEn 3,600 mg/day, *n* = 56 GEn 2,400 mg/day, *n*= 62 GEn 1,200 mg/day, *n* = 66 PGB 300 mg/day, *n* = 120 placebo). One subject in the GEn 3,600 mg group, who was randomized in error, did not take study medication and therefore was excluded from the Safety population. Of the 420 subjects in the Safety population, all were included in the ITT population.

The majority of subjects enrolled in the study were white (80%) and male (59%). Mean age ranged from 57.5–60.8 years across treatment groups. Across treatment groups, the majority of subjects (61% [GEn 2,400 mg/day], 66% [GEn 3,600 mg/day], 74% [GEn 1,200 and PGB], and 78% [PBO]) were obese as defined by a BMI > 30 kg/m^2.

Demographics and baseline characteristics were similar among treatment groups (Table 2).

Efficacy—Pain Measures

The primary efficacy endpoint was the change from baseline to EOMT for the mean 24-hour average pain intensity score based on an 11-point PI-NRS. A decreased mean 24-hour average pain intensity score at EOMT, as compared to baseline, was noted in all treatment groups (Table 3, Figure 1).

For the primary analysis (using LOCF data), there were no statistically significant differences when comparing each active daily dose of GEn (1,200 mg, 2,400 mg, and 3,600 mg) vs. placebo, *P* = 0.295, 0.946, and 0.105, respectively, at EOMT. The unadjusted *P*-values (ie not adjusted for multiple comparisons of active treatment vs. placebo) were 0.295, 0.946, and 0.052, respectively.

Consistent with the primary LOCF analysis, the supportive analyses of the ITT population using BOCF, BOCF/LOCF hybrid, OC, the MMRM analysis of the ITT population using OC data, and the PP population analyses all resulted in a decreased 24-hour pain intensity score at EOMT, as compared with placebo (Table 4). When considering the BOCF and MMRM

Table 2. Demographics and Baseline Characteristics (Safety Population)

			Number (%) of Subjects			
	PBO N = 120	GEn 1,200 mg N = 62	GEn 2,400 mg N = 56	GEn 3,600 mg N = 116	PGB 300 mg N = 66	Total N = 420
Age						
Mean (SD)	60.1(10.63)	57.5 (10.32)	60.8 (8.97)	57.5 (9.87)	57.7(10.59)	58.7 (10.20)
Range	29–85	32–77	33–78	35–79	35–79	29–85
Age group						
≤ 65 years	82 (68%)	44 (71%)	39 (70%)	90 (78%)	50 (76%)	305 (73%)
> 65 years	38 (32%)	18 (29%)	17 (30%)	26 (22%)	16 (24%)	115 (27%)
Sex						
Female	47 (39%)	28 (45%)	19 (34%)	45 (39%)	32 (48%)	171 (41%)
Male	73 (61%)	34 (55%)	37 (66%)	71 (61%)	34 (52%)	249 (59%)
Race						
White*	98 (82%)	46 (74%)	47 (85%)	90 (79%)	52 (81%)	333 (80%)
BMI						
≤ 30	27 (23%)	16 (26%)	22 (39%)	39 (34%)	17 (26%)	121 (29%)
> 30	93 (78%)	46 (74%)	34 (61%)	77 (66%)	49 (74%)	299 (71%)
Baseline 24-hour pain score						
Mean	6.49	6.64	6.26	6.48	6.51	N/A
(SD)	(1.26)	(1.47)	(1.22)	(1.43)	(1.27)	
Range	4.0–10.0	4.0–9.4	4.0–9.6	4.0–10.0	4.0–9.3	
Baseline 24-hour pain score						
4 to < 6.5	61 (51%)	25 (40%)	32 (57%)	63 (54%)	33 (50%)	214 (51%)
6.5 to 10	59 (49%)	37 (60%)	24 (43%)	53 (46%)	33 (50%)	206 (49%)
Creatinine Clearance, est. (mL/min)						
Mean	111.3	115.3	107.1	119.6	121.5	N/A
(SD)	(38.09)	(40.49)	(39.35)	(41.94)	(47.57)	
Range	45–296	31–262	43–222	45–249	47–299	

*Other races were primarily African American/African Heritage.
N/A, not applicable

Table 3. Change from Baseline in 24-Hour Average Pain Intensity Score at End of Maintenance Treatment (ITT Population, LOCF Imputation)

Time Period	Parameter	PBO N = 120	GEn 1,200 mg N = 62	GEn 2,400 mg N = 56	GEn 3,600 mg N = 116	PGB 300 mg N = 66
Baseline	Mean	6.49	6.64	6.26	6.48	6.51
Change	Mean	−2.09	−2.55	−1.90	−2.54	−1.66
from	SD	2.069	2.535	2.049	2.423	1.833
Baseline	Median	−1.59	−1.71	−1.61	−2.15	−1.54
to	Min	−7.5	−8.4	−6.1	−8.0	−7.1
EOMT[1]	Max	1.8	1.0	4.3	4.3	2.2

End of maintenance treatment.
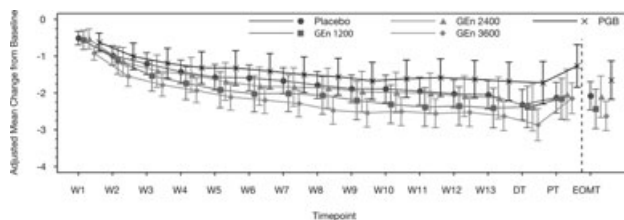
Figure 1. Adjusted mean (95% CI) change from baseline in 24-hour average pain intensity by week and at the EOMT (ITT, LOCF).

analysis, the magnitude of the improvement was greater in the GEn 3,600 mg/day treatment group than in the placebo treatment group, with the confidence intervals (not multiplicity-adjusted) indicating a benefit for GEn 3,600 mg/day over placebo.

Per the predefined testing strategy, GEn 1,200 mg vs. placebo was only to be tested if both GEn 2,400 mg and GEn 3,600 mg were significantly better than placebo at an alpha (α) level of 0.05. Thus, the results for the 1,200 mg group are included in Table 4 for reference and should only be considered descriptive. The active control, PGB (300 mg/day), did not differentiate from placebo. Neither the method of imputation, statistical analysis technique, nor the population had a significant impact on the primary efficacy measure.

The secondary efficacy analyses were performed on the ITT population, and as shown in Tables 5 and 6, overall, the analyses of the secondary endpoints showed comparable results across treatment groups. Additionally, the time to sustained improvement was defined as the time to the first of two or more consecutive days of at least 2-points reduction in the 24-hour average pain intensity score relative to baseline. Fifty percent of subjects in the GEn 3,600 mg treatment group achieved sustained improvement within 15 days of first dose of investigational product as compared to PBO (24 days),

Table 4. Treatment Difference vs. Placebo for Change from Baseline in Mean 24-Hour Average Pain Intensity Score at End of Maintenance Treatment (LOCF, BOCF, BOCF/LOCF Hybrid, OC, MMRM, PP Population)

Population (Imputation Method)	GEn 1,200 mg N = 62	GEn 2,400 mg N = 56	GEn 3,600 mg N = 116	PGB 300 mg N = 66
ITT (LOCF)				
n	62	56	116	66
Adj. mean diff vs. Placebo	−0.35	−0.02	−0.55	0.43
95% CI	(−1.02, 0.31)	(−0.71, 0.66)	(−1.10, 0.01)	(−0.22, 1.08)
Adj. *P*-value*	0.295	0.946	0.105	NA
ITT (BOCF)				
n	62	56	116	66
Adj. mean diff vs. Placebo	−0.29	0.02	−0.58	0.41
95% CI	(−0.96, 0.37)	(−0.67, 0.70)	(−1.13, −0.02)	(−0.24, 1.07)
ITT (BOCF/LOCF hybrid)				
n	62	56	116	66
Adj. mean diff vs. Placebo	−0.36	−0.03	−0.56	0.43
95% CI	(−1.03, 0.30)	(−0.71, 0.66)	(−1.12, −0.01)	(−0.22, 1.08)
ITT (OC)				
n	59	53	115	65
Adj. mean diff vs. Placebo	−0.37	−0.01	−0.56	0.43
95% CI	(−1.05, 0.31)	(−0.71, 0.70)	(−1.12, 0.01)	(−0.23, 1.09)
Per-protocol (LOCF)				
n	49	42	93	53
Adj. mean diff vs. Placebo	−0.39	−0.07	−0.69	0.42
95% CI	(−1.15, 0.37)	(−0.88, 0.73)	(−1.32, −0.06)	(−0.33, 1.16)
MMRM (OC)				
n	59	53	115	65
Adj. mean diff vs. Placebo	−0.37	−0.03	−0.50	0.45
95% CI	(−0.92, 0.19)	(−0.60, 0.55)	(−0.97, −0.04)	(−0.1. 0.99)

A negative treatment difference indicates benefit, relative to placebo.
*Adjusted *P*-values are valid for inference of the LOCF analysis. Adjustments to *P*-values were made based on multiple treatment arms.

GEn 1,200 mg (25 days), GEn 2,400 mg (22 days), and PGB 300 mg (29 days) treatment groups.

Safety and Tolerability

The majority of subjects across all treatment groups reported at least one TEAE. Overall, the rate of AEs (any event) reported across the GEn groups and the PGB group was comparable. The most commonly reported TEAEs that occurred at a rate ≥ 5% in any active treatment group included dizziness, somnolence, nausea, and peripheral edema (Table 7).

The majority of subjects in each treatment group completed the study. A slightly higher percentage of subjects in the GEn daily doses of 2,400 mg and 3,600 mg withdrew from the study, as compared with the other treatment groups (Figure 2). This difference was driven by a higher rate of AE withdrawals in the higher dose GEn treatment groups (21% in the GEn 2,400 mg treatment group and 18% in the GEn 3,600 mg treatment group). The GEn 3,600 mg treatment group had the smallest proportion of subjects withdraw from the study due to protocol deviations. For all other categories of withdrawal, the treatment groups were comparable in the percentage of subjects withdrawn.

No AE led to the withdrawal of > 5% of subjects in any treatment group. Additionally, there was no consistent pattern of AEs related to dose or treatment across treatment groups. There was one report of suicidal ideation in the study; it occurred in the GEn 3,600 mg group. It was reported as moderate in severity, not serious, and was considered to be related to the investigational product by the investigator. The subject had no history of psychiatric conditions including suicidal ideation, behavior, or self-harm. Reported stressors included job loss and domestic stress. The event occurred 51 days after starting GEn and lasted 1 day. GEn treatment was discontinued, and the likelihood of reoccurrence was reported as unlikely.

During the study, 22 subjects reported 29 nonfatal SAEs and no clear differences were noted between treatment groups. No deaths occurred during this study.

There were no clinically significant mean changes in blood pressure or HR in the GEn, PGB, or placebo treatment groups. At the end of maintenance treatment, subjects in the PGB treatment group experienced the most weight gain. Of the GEn groups, weight gain increased by dose with subjects in the GEn 3,600 mg/day group experiencing the most weight gain and subjects in the GEn 1,200 mg/day group experienced the least gain. Subjects in the placebo group showed the least change in weight across all treatment groups. The proportion of subjects who had weight gain of at least 7% at any visit postrandomization was greatest in the PGB group (15%), followed by the GEn 3,600 mg group (11%) compared with the GEn 2,400 mg (7%), GEn 1,200 mg (5%) and PBO (3%). There were no systematic changes noted in laboratory parameters or ECG findings across the treatment groups.

Pharmacokinetics/Pharmacodynamics

Gabapentin plasma concentration data in DPN subjects were collected in accordance with the protocol. Only four subjects were excluded from the PK analysis. The distribution of sampling times during the treatment was homogeneous between doses, which allowed capture of

Table 5. Secondary Outcome Measures

	GEn 1,200 mg vs. placebo		GEn 2,400 mg vs. placebo		GEn 3,600 mg vs. placebo		PGB 300 mg vs. placebo	
	Adj Mean Diff	95% CI	Adj Mean Diff	95% CI	Adj Mean Diff	95% CI	Adj Mean Diff	95% CI
Treatment difference in change from baseline pain intensity and sleep endpoints at EOMT (LOCF)								
Daytime avg pain*	−0.28	(−0.94, 0.38)	0.00	(−0.68, 0.68)	−0.47	(−1.02, 0.08)	0.57	(−0.08, 1.21)
Daytime worst pain*	−0.01	(−0.72, 0.70)	0.08	(−0.65, 0.82)	−0.54	(−1.13, 0.05)	0.71	(0.02, 1.41)
Nighttime avg pain*	−0.16	(−0.84, 0.52)	−0.05	(−0.76, 0.66)	−0.72	(−1.29, −0.15)	0.16	(−0.51, 0.83)
Nighttime worst pain*	0.02	(−0.70, 0.74)	0.00	(−0.74, 0.75)	−0.75	(−1.35, −0.14)	0.39	(−0.31, 1.10)
Current morning pain*	−0.19	(−0.83, 0.46)	−0.05	(−0.72, 0.62)	−0.50	(−1.04, 0.04)	0.40	(−0.24, 1.03)
Current evening pain*	−0.05	(−0.71, 0.60)	0.08	(−0.60, 0.76)	−0.47	(−1.02, 0.08)	0.54	(−0.11, 1.18)
Sleep interference*	−0.19	(−0.91, 0.53)	−0.10	(−0.85, 0.64)	−0.66	(−1.26, −0.06)	0.11	(−0.60, 0.82)
Sleep time, hours*	−0.02	(−0.34, 0.29)	−0.15	(−0.47, 0.18)	−0.00	(−0.26, 0.26)	0.09	(−0.22, 0.40)
Nighttime awakenings due to pain*	−0.04	(−0.34, 0.25)	0.07	(−0.24, 0.38)	−0.10	(−0.34, 0.15)	−0.12	(−0.41, 0.18)
Total nighttime awakenings*	−0.25	(−0.59, 0.08)	−0.21	(−0.56, 0.13)	−0.25	(−0.53, 0.03)	−0.47	(−0.80, −0.14)
% of days using sleep medications*	5.93	(−4.06, 15.92)	−2.53	(−12.90, 7.80)	−5.65	(−14.00, 2.72)	1.55	(−8.29, 11.39)
After 50ft Walk†	0.06	(−0.20, 0.32)	0.02	(−0.26, 0.31)	−0.13	(−0.35, 0.08)	0.21	(−0.05, 0.47)
BPI Severity†	−0.3	(−0.96, 0.44)	−0.3	(−1.06, 0.47)	−0.7	(−1.29, −0.12)	0.4	(−0.28, 1.08)
BPI Interference†	−0.0	(−0.76, 0.69)	−0.2	(−0.95, 0.63)	−0.6	(−1.16, 0.04)	0.1	(−0.59, 0.82)
Treatment difference in change from baseline in efficacy and health outcomes at EOMT† (LOCF)								
SF-36 Physical Component Score	0.3	(−1.92, 2.62)	0.6	(−1.88, 3.06)	1.4	(−0.46, 3.31)	0.6	(−1.60, 2.83)
SF-36 Mental Component Score	−2.1	(−5.09, 0.90)	−1.0	(−4.24, 2.30)	−0.8	(−3.34, 1.64)	−1.8	(−4.68, 1.17)
POMS-B Tension-Anxiety	0.4	(−0.59, 1.38)	0.2	(−0.84, 1.32)	0.0	(−0.80, 0.85)	0.6	(−0.34, 1.59)
POMS−B Depression-Rejection	0.4	(−0.66, 1.41)	−0.1	(−1.21, 1.05)	0.2	(−0.63, 1.09)	0.9	(−0.12, 1.90)
POMS-B Anger-Hostility	−0.3	(−1.41, 0.78)	−0.0	(−1.21, 1.18)	0.2	(−0.66, 1.15)	0.2	(−0.88, 1.25)
POBS-B Vigor-Activity	−0.6	(−1.73, 0.46)	−0.5	(−1.65, 0.73)	0.1	(−0.81, 1.00)	−0.9	(−1.98, 0.16)
POMS-B Fatigue-Inertia	0.4	(−0.88, 1.64)	−0.3	(−1.67, 1.09)	−0.3	(−1.31, 0.79)	0.8	(−0.46, 2.00)
POMS-B Confusion-Bewilderment	0.4	(−0.27, 1.14)	0.1	(−0.63, 0.91)	0.3	(−0.31, 0.86)	0.0	(−0.69, 0.70)
Treatment difference in change from baseline at EOMT† (LOCF)								
NPS 10	0.49	(−5.96, 6.93)	−3.33	(−10.3, 3.69)	−6.57	(−12.0, −1.18)	2.76	(−3.55, 9.07)
NPS 8	0.90	(−5.50, 7.29)	−3.11	(−10.1, 3.85)	−6.41	(−11.8, −1.05)	2.54	(−3.72, 8.80)
NPS NA	0.49	(−6.24, 7.22)	−3.49	(−10.8, 3.84)	−6.98	(−12.6, −1.34)	3.74	(−2.85, 10.33)
NPS 4	−0.36	(−7.49, 6.78)	−4.61	(−12.4, 3.16)	−7.30	(−13.3, −1.32)	4.48	(−2.51, 11.47)
SF-MPQ Total	−0.70	(−3.64, 2.24)	−0.90	(−4.10, 2.29)	−1.71	(−4.14, 0.73)	1.84	(−1.00, 4.69)
SF-MPQ Sensory	−0.58	(−2.88, 1.71)	−1.06	(−3.56, 1.43)	−1.25	(−3.15, 0.65)	1.52	(−0.70, 3.74)
SF-MPQ Affective	−0.02	(−0.86, 0.82)	0.19	(−0.73, 1.10)	−0.44	(−1.14, 0.26)	0.37	(−0.44, 1.18)
Daily Dose of Rescue Meds (mg) *	90.36	(−158, 338.6)	159.48	(−97.4, 416.4)	33.46	(−175, 242.2)	15.92	(−228, 259.6)
Proportion of PGI/CGI responders at EOMT† (LOCF)	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
PGIC	0.8	(0.40, 1.65)	1.9	(0.88, 3.97)	1.5	(0.86, 2.75)	0.9	(0.46, 1.83)
CGIC	0.9	(0.47, 1.88)	1.8	(0.88, 3.89)	1.9	(1.08, 3.47)	0.7	(0.34, 1.40)

EOMT, end of maintenance treatment; LOCF, last observation carried forward.
*The EOMT value reflects the seven postbaseline days prior to or on the date of last study medication or the week 13/withdrawal visit, whichever comes first, with imputation.
†The EOMT value reflects the week 13 assessment; for participants without a week 13 visit, this value reflects the assessment collected at the withdrawal visit, as long as it occurred within one day of last dose of study medication;
otherwise this is the last postbaseline assessment collected on or before the date of last dose of study medication and may include data collected during the up-titration period.

Table 6. Responder Rates for 24-Hour Average Pain Intensity at EOMT (LOCF), *n* (%)

Percentage Reduction from Baseline	Placebo (*N* = 120)	GEn 1,200 mg (*N* = 62)	GEn 2,400 mg (*N* = 56)	GEn 3,600 mg (*N* = 116)	PGB 300 mg (*N* = 66)
≥ 0	103 (86%)	55 (89%)	50 (89%)	101 (87%)	55 (83%)
≥ 10%	86 (72%)	43 (69%)	42 (75%)	91 (78%)	42 (64%)
≥ 20%	73 (61%)	36 (58%)	34 (61%)	78 (67%)	36 (55%)
≥ 30%	57 (48%)	31 (50%)	25 (45%)	66 (57%)	28 (42%)
≥ 40%	46 (38%)	28 (45%)	19 (34%)	55 (47%)	20 (30%)
≥ 50%	35 (29%)	26 (42%)	15 (27%)	46 (40%)	14 (21%)
≥ 60%	26 (22%)	21 (34%)	11 (20%)	41 (35%)	9 (14%)
≥ 70%	15 (13%)	17 (27%)	6 (11%)	25 (22%)	5 (8%)
≥ 80%	11 (9%)	11 (18%)	5 (9%)	17 (15%)	4 (6%)
≥ 90%	4 (3%)	5 (8%)	2 (4%)	8 (7%)	3 (5%)
100%	3 (3%)	4 (6%)	1 (2%)	5 (4%)	3 (5%)

Table 7. Most Common (at Least 5%) Treatment-Emergent Adverse Events (Safety Population)

	Number (%) of Subjects				
Preferred Term	Placebo *N* = 120	GEn 1,200 mg *N* = 62	GEn 2,400 mg *N* = 56	GEn 3,600 mg *N* = 116	PGB 300 mg *N* = 66
Any event	79 (66)	45 (73)	38 (68)	86 (74)	47 (71)
Dizziness	7 (6)	9 (15)	8 (14)	16 (14)	9 (14)
Somnolence	5 (4)	2 (3)	7 (13)	14 (12)	9 (14)
Nausea	9 (8)	7 (11)	4 (7)	7 (6)	3 (5)
Peripheral edema	5 (4)	2 (3)	0	11 (9)	11 (17)
Headache	9 (8)	3 (5)	4 (7)	4 (3)	6 (9)
Muscle spasms	4 (3)	6 (10)	0	11 (9)	3 (5)
Diarrhea	6 (5)	3 (5)	2 (4)	6 (5)	5 (8)
Urinary tract infection	5 (4)	3 (5)	4 (7)	6 (5)	4 (6)
Constipation	4 (3)	3 (5)	4 (7)	4 (3)	6 (9)
Fatigue	3 (3)	3 (5)	3 (5)	5 (4)	4 (6)
Arthralgia	5 (4)	1 (2)	2 (4)	5 (4)	3 (5)
Nasopharyngitis	5 (4)	1 (2)	2 (4)	4 (3)	3 (5)
Pain in extremity	2 (2)	1 (2)	4 (7)	6 (5)	2 (3)
Vision blurred	5 (4)	0	3 (5)	2 (2)	3 (5)
Weight increased	1 (< 1)	0	2 (4)	5 (4)	5 (8)
Back pain	3 (3)	1 (2)	1 (2)	3 (3)	3 (5)
Increased appetite	4 (3)	0	3 (5)	1 (< 1)	3 (5)
Dry mouth	4 (3)	0	4 (7)	1 (< 1)	1 (2)
Disturbance in attention	2 (2)	2 (3)	0	2 (2)	3 (5)
Vomiting	3 (3)	3 (5)	1 (2)	2 (2)	0
Bronchitis	1 (< 1)	3 (5)	1 (2)	0	1 (2)
Excoriation	0	1 (2)	1 (2)	1 (< 1)	3 (5)
Hypoesthesia	1 (< 1)	1 (2)	1 (2)	0	3 (5)
Paresthesia	0	2 (3)	1 (2)	0	3 (5)
Fall	0	3 (5)	1 (2)	1 (< 1)	0

All AEs occurred more frequently than placebo in at least one active treatment arm.

the PK profile of gabapentin during the dosing interval at steady state.

An exposure–pain reduction response was established for gabapentin following administration of GEn. The pharmacodynamic effects of GEn were modelled as a linear function of daily gabapentin exposure (AUC_{0-24}). After placebo correction, the net drug effect was small, as shown in Figure 3. For the highest gabapentin $AUC0-24_{ss}$ (312–758 μg*h/mL) obtained in the study, the median net effect was a 0.9-point reduction in pain score on a [0–10] scale. The net drug response ranged

0.4 to 3; four subjects had a net drug effect > 3. However, these subjects were considered outliers.

DISCUSSION

In this randomized clinical study of patients with neuropathic pain associated with DPN, all treatment groups experienced a reduction in pain intensity scores (baseline to EOMT) as measured on the 11-point PI-NRS with scores ranging from −1.66 with PGB to −2.54 with GEn 3,600 mg. However, comparisons
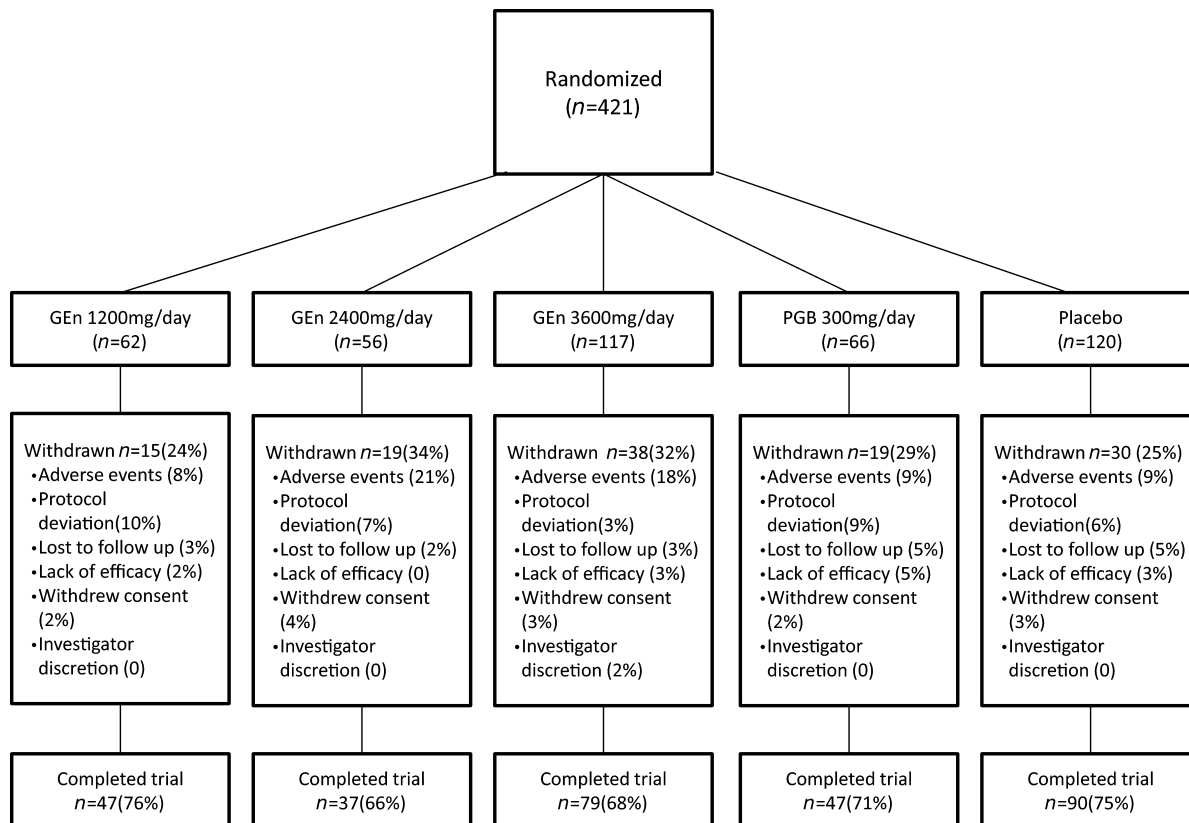
Figure 2. Summary of subject disposition and reasons for premature withdrawal (randomized population).
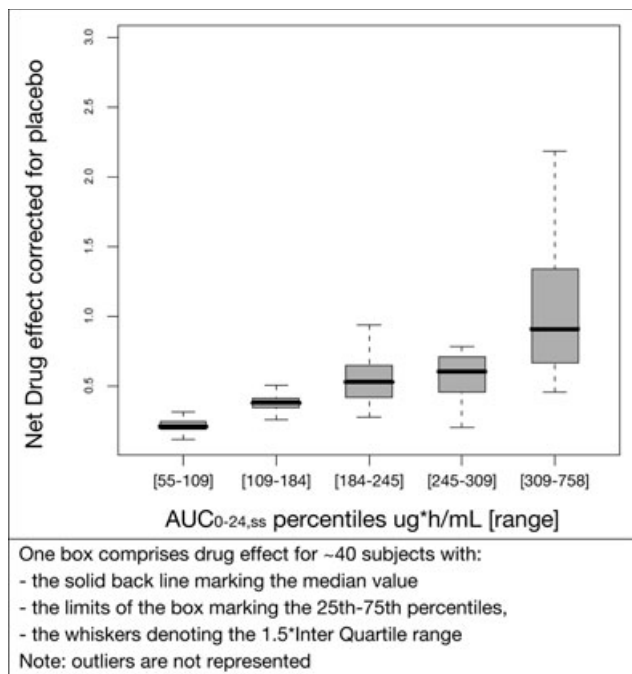
Figure 3. Drug effect (corrected for placebo) estimated as a function of gabapentin systemic exposure (PK population).

between GEn and placebo failed to reach statistical significance with adjusted mean differences ranging from -0.02 (GEn 2,400 mg; $P = 0.946$) to -0.55 (GEn 3,600 mg; $P = 0.105$). The results were consistent across multiple methods of adjusting for missing values (ie LOCF, BOCF, BOCF/LOCF hybrid, OC [ITT, Per-protocol and MMRM]). When compared to placebo, the active-control arm of the study, PGB 300 mg, also failed to reach statistical significance with the adjusted mean difference actually favouring the placebo treatment group.

Gabapentin, which is approved for the treatment of postherpetic neuralgia (PHN), has been prescribed extensively over the past 15+ years for the treatment of neuropathic pain and has been investigated in numerous neuropathic and nonneuropathic pain conditions[11]. While gabapentin has demonstrated efficacy in reduction in perioperative pain and opioid use, several reviews of pharmacological management in neuropathic pain have concluded that gabapentin should be considered a first-line drug in neuropathic pain conditions[12,13]. In a well-designed prospective, randomized, double-blind, placebo-controlled study, Backonja et al. examined the

efficacy of gabapentin in neuropathic pain associated with diabetic peripheral neuropathy (DPN). Gabapentin demonstrated significant efficacy in this study of 165 patients with DPN; pain in the gabapentin group decreased from 6.4 to 3.9 (Likert scale: 0–10) vs. placebo, 6.5 to 5.1 ($P < 0.001$), and all secondary endpoints statistically favored gabapentin over placebo[14].

A study of DPN patients ($n = 40$), by Gorson et al., failed to show efficacy in a placebo-controlled, double-blind, crossover design. A secondary endpoint, the McGill pain questionnaire, demonstrated statistically significant benefit of gabapentin vs. placebo ($P = 0.03$). The dose of gabapentin did not exceed the daily dose of 900 mg[15].

Numerous drugs studied in neuropathic pain have reported negative outcomes. It has often been difficult to interpret these results when juxtaposed with other positive trials or clinical practice[12,13]. Are there differences in neuropathic disease states that might explain the conflicting reports? Dworkin et al. recently compared clinical trial results in the two most commonly studied neuropathic disease states: DPN and PHN. The authors found that the placebo group improvements were greater in painful DPN trials when compared with PHN trials. When compared with results in groups receiving active medication, the placebo benefits could not be attributed to greater overall improvement in subjects with DPN[12].

Pregabalin and duloxetine have both received regulatory approval for the treatment of DPN. As stated above, gabapentin had mixed efficacy trials in two well-designed RCTs. However, gabapentin is listed as first-line treatment for DPN in several guideline publications. Many clinicians, following these guidelines, have reported and discussed the benefits of gabapentin in their patients with DPN.

Given the backdrop described above, one should be well acquainted with the nuances of clinical trials and drug development. These nuances appear enhanced in the particular population of patients with DPN. The current trial of gabapentin enacarbil (GEn) clearly failed to meet its primary efficacy endpoint or any of its secondary endpoints. An active comparator, pregabalin (approved for the indication of DPN), performed as poorly or worse compared to the study drug. How does one interpret these results? Does this represent a failed trial or a failed drug (negative trial)?

In the current study of GEn, subjects receiving placebo reported possibly significant pain relief (> 2

point reduction on a 0–10 point Likert scale) at the end of the maintenance phase (13 weeks of double-blind conditions). While this level of placebo response has occurred in other chronic pain trials, it presents an enormous burden for an active drug to overcome. There may be several reasons to explain this degree of placebo response.

First, the natural history of painful diabetic peripheral neuropathy waxes and wanes. Some patients develop spontaneous improvements in their pain, more commonly early in the disease process. If more of these patients happen to be receiving placebo, they will accurately report significant improvements in their pain, despite the lack of a pharmacologically active compound being received. Results would expect to skew in favor of the placebo group.

Second, there are differences between PHN and DPN regarding underlying pathophysiologic mechanisms. DPN is a disease of the peripheral nervous system while PHN patients often have lesions in the dorsal horn of the spinal cord. It has been hypothesized that intact descending inhibitory pathways in the spinal cord dorsal horn are required for the placebo response[16]. This could explain the differences in placebo responses seen between these two study groups and further explain the placebo response seen in the current trial.

Third, the current study randomized subjects into one of five treatment groups. Randomization occurred such that subjects had only a two in seven chance of receiving placebo. As this information was provided in the informed consent form, subjects knew that the chances of receiving an active compound were greater than 70%. A familiar maxim states, "Results follow expectations." Unknowingly, subjects receiving placebo could overstate the analgesic efficacy they perceived during the trial.

The current study was designed with a placebo group, three fixed doses of GEn, and the active comparator, pregabalin (PGB) for various reasons. The US FDA routinely wants to know the minimum effective dose of a drug. Phase II clinical trials are commonly designed to study doses and are often referred to as dose ranging studies. Earlier work had suggested that 1,200 mg/day of GEn would be inferior to the higher doses. Maximally tolerated dose is another concept often explored in Phase II studies. The 3,600 mg daily dose of GEn was thus included in the current trial as the highest dose. To adequately explore the dose response of GEn in subjects with DPN, it was necessary to include several groups in the study design.

The active comparator, PGB, was included in the current trial to provide a descriptive assessment of the assay sensitivity of the study. However, this added an additional treatment group who received a pharmacologically active drug and possibly increased the placebo response stated above. In retrospect, the decision to include pregabalin may have emphatically demonstrated the failed aspect of this trial. Pregabalin has performed very well in DPN and has an FDA approved indication in DPN. The fact that pregabalin performed worse than placebo in the current trial further supports the idea of flaws in either the trial design or the specific population included in the trial.

In conclusion, one will never unequivocally know whether the current results represent a failed trial or a failed drug. Previous studies of gabapentin in DPN and the overwhelming clinical impression of analgesic efficacy of this compound in treating patients with DPN support the notion that these results support a failed trial. Previous pharmacologic information of GEn supports that gabapentin would have been in the plasma in similar and higher concentrations to studies with the parent compound. Future research will undoubtedly help answer these lingering questions.

ACKNOWLEDGEMENTS

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Lamotrigine reduces painful diabetic neuropathy

A randomized, controlled study

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Article abstract—*Objective:* To study the efficacy of lamotrigine in relieving the pain associated with diabetic neuropathy. *Methods:* The authors randomly assigned 59 patients to receive either lamotrigine (titrated from 25 to 400 mg/day) or placebo over a 6-week period. Primary outcome measure was self-recording of pain intensity twice daily with a 0 to 10 numerical pain scale (NPS). Secondary efficacy measures included daily consumption of rescue analgesics, the McGill Pain Questionnaire (MPQ), the Beck Depression Inventory (BDI), the Pain Disability Index (PDI), and global assessment of efficacy and tolerability. *Results:* Twenty-four of 29 patients (83%) receiving lamotrigine and 22 of 30 (73%) patients receiving placebo completed the study. Daily NPS in the lamotrigine-treated group was reduced from 6.4 ± 0.1 to 4.2 ± 0.1 and in the control group from 6.5 ± 0.1 to 5.3 ± 0.1 ($p < 0.001$ for lamotrigine doses of 200, 300, and 400 mg). The results of the MPQ, PDI, and BDI remained unchanged in both groups. The global assessment of efficacy favored lamotrigine treatment over placebo, and the adverse events profile was similar in both groups. *Conclusions:* Lamotrigine is effective and safe in relieving the pain associated with diabetic neuropathy.

Abnormal neural firing may be a major cause of neuropathic pain.[1] Spontaneous activity of primary afferent neurons was found in diabetic rats[2] and in the dorsal horn of rats with experimental peripheral neuropathy.[3] Furthermore, there is now evidence that excitatory amino acids, particularly glutamate, play a key role in dorsal horn spinal hyperexcitability by acting at the NMDA receptor.[4,5]

The antiepileptic agent lamotrigine has at least two antinociceptive properties: it stabilizes the neural membrane through blocking activation of voltage-sensitive sodium channels and it inhibits the presynaptic release of glutamate.[6] Animal studies have demonstrated the ability of lamotrigine to reduce hyperalgesia in rats with streptozotocin-induced diabetes.[7,8] Open studies in humans have suggested that lamotrigine may reduce painful diabetic neuropathy,[9] trigeminal neuralgia,[10] symptoms of complex regional pain syndrome type 1,[11] and chronic refractory neuropathic pain of mixed etiologies.[12] Painful HIV-associated neuropathy and central poststroke pain have been relieved by lamotrigine but not by placebo in recent controlled trials.[13,14] We report a trial of the analgesic efficacy of lamotrigine in painful diabetic neuropathy. Preliminary results were reported earlier.[15]

Methods. *Patients.* The study was approved by the Ethics Committee of Rambam Medical Center in Haifa,

Israel. All patients provided written informed consent before enrollment. Patients were considered eligible if 1) they had an established diagnosis of diabetes mellitus (type 1 or 2); 2) no change had been made in their antihyperglycemic medications within 3 weeks before screening; 3) evidence of peripheral neuropathy was indicated by at least two of the three following measures: a) medical history, b) neurologic examination, or c) abnormal nerve conduction test results; 4) pain attributed to diabetic neuropathy had been present for at least 6 months; and 5) a mean pain intensity of at least 4 on an 11-point numerical pain scale (NPS; 0 to 10; 0 means no pain, 10 means the worst imaginable pain) was recorded twice daily (morning and evening) during the week before randomization. Exclusion criteria included 1) age younger than 18 or older than 75 years; 2) impaired renal or liver function; 3) known epilepsy; 4) presence of other painful conditions; 5) receipt of anticonvulsants, antidepressants, or membrane-stabilizing agents for reasons other than pain relief, or use of opioids; and 6) participation in any clinical trial within 30 days before screening.

Design. The study was a randomized, double-blinded, placebo-controlled, parallel- group, single-center trial and consisted of three phases: a 7-day screening phase, an 8-week, double-blinded treatment phase, and a 2-week post-treatment phase.

Screening phase. Letters providing information about the study were sent to primary care physicians, neurologists, diabetes clinics, and pain clinics in northern Israel. Ads were published in the local newspapers informing the public about the opportunity for self-referral. Study eligi-

bility was determined in the first two visits: during the first visit, informed consent and medical history were obtained, medical and neurologic examinations were performed, and blood samples for liver and kidney function tests, hemoglobin A1c (HbA1c), and fasting glucose levels were drawn. Subjects meeting the initial inclusion criteria were instructed to record their pain intensity and their consumption of rescue analgesics in a daily diary. Patients who were taking analgesics (including anticonvulsants, antidepressants, membrane stabilizers, and opioids) were requested to discontinue the use of these drugs for at least 3 days before beginning the use of the diary. In the second visit, final eligibility was determined by reviewing the diaries and the results of the blood tests.

Randomization. Only patients who met all inclusion criteria were randomly assigned to receive either lamotrigine or a placebo. Randomization was done in blocks of four according to a computer-generated random code in a double-blinded fashion.

Treatment phase. Treatment was initiated at a daily dose of 25 mg for 2 weeks, increased to 50 mg/day for 2 more weeks, and subsequently to 100, 200, 300, and 400 mg/day, each dose for an additional week. The dosing schedule was once daily during the first 2 weeks and twice daily for the remaining 6 weeks. Patients in the placebo group received equal numbers of identical-looking placebo tablets according to the same schedule. Both the lamotrigine and the placebo tablets were kindly supplied by Glaxo-Wellcome, USA. Patients were allowed to use rescue medications, including simple analgesics (paracetamol or dipyrone) and nonsteroidal anti-inflammatory drugs.

Post-treatment phase. After the 8-week treatment period, study medications were discontinued. Patients were allowed to continue the use of rescue medications and were requested to continue the daily diary for an additional 2 weeks.

Efficacy and safety measures. The primary efficacy parameter was a pain intensity score recorded by patients twice daily (morning and evening), using the 0 to 10 NPS.[16] Patients were instructed to record their "present pain intensity" and not to take any rescue medication for at least 2 hours before the recording time. Secondary efficacy parameters included the daily recording of rescue analgesic consumption, as well as completion of the McGill Pain Questionnaire (MPQ),[17] the Beck Depression Inventory (BDI),[18] and the Pain Disability Index (PDI),[19] both before and at the end of the treatment phase. In addition, patients were requested at the end of the treatment phase to complete a global assessment of both efficacy and tolerability of the drug that they were receiving, using a 0 to 10 scale. For each parameter, a score of 8 to 10 was regarded as high, 4 to 7 as moderate, and 0 to 3 as low. Plasma glucose and HbA1C levels also were measured before and at the end of the treatment phase. Patients were seen at four separate office visits during the treatment period and at the end of the post-treatment phase for dispensing/collecting the study medications and diaries as well as for assessment of adverse effects.

Statistical analysis. Based on previous studies with painful diabetic neuropathy, a 20% to 25% difference in efficacy between lamotrigine and placebo was considered to have clinical significance. A sample size of 25 subjects per group was found to be large enough to provide 80%

power for detecting such a difference according to the Lehr formula.[20] Statistical analysis was performed with SAS (SAS Institute, Cary, NC). The daily NPS were averaged across weeks and were analyzed by repeated-measures analysis of variance. Comparisons of the pretreatment (baseline) week with each subsequent week of the treatment and the post-treatment phases were performed using Dunnett's test. MPQ, BDI, and PDI, as well as glucose and HbA1C levels, were evaluated by paired t-test, comparing baseline with end-of-treatment scores. Sex differences and global assessment scores were compared by chi-square. Statistical significance was assigned at the $p = 0.05$ level. Data are presented as mean $\pm$ SEM.

Results. *Patients.* Fifty-nine of 160 screened patients were randomized to receive either active treatment (29) or placebo (30). In the lamotrigine-treated group, two patients were withdrawn because of lack of compliance (incomplete daily diaries) and were not included in the final analysis. Three other patients withdrew consent: two because of the occurrence of adverse events, and one who requested to leave the study after 4 weeks of treatment for "personal reasons." Data on efficacy (NPS) from those three subjects were included in the analyses up to the point of their leaving the study. In the placebo-treated group, four patients were withdrawn from the study and were not included in the final analysis, three because of lack of compliance (incomplete diaries) and one because of protocol violation (opened the emergency blinding code). Four other subjects did not complete the treatment phase for the following reasons: one had a car accident in the fifth week of treatment, two because of adverse events, and one asked to stop her participation in the study for "personal reasons" during the fifth week of treatment. Data from those four subjects up to the point of leaving the study were included in the analyses. Thus, data related to baseline diabetes and pain measures, demographics, primary outcome measures, and adverse events were available from 53 subjects (lamotrigine, 27; placebo, 26). The analysis of the secondary outcome measures (MPQ, PDI, BDI, and global assessment) included only the 46 subjects (lamotrigine, 24; placebo, 22) who completed the entire treatment period.

The two groups were not significantly different from each other in the number of patients enrolled, sex ratio, weight, type of diabetes, and initial diabetes severity, as measured by HbA1c and fasting blood glucose. However, the duration of diabetes in the lamotrigine-treated group was significantly longer than that in the placebo-treated group (13.9 $\pm$ 1.7 years versus 9.6 $\pm$ 1.1 years). All patients had distal symmetric pain involving the legs in a stocking-like distribution. Loss of sensation was noted by 24 subjects in the lamotrigine-treated group and by 21 in the placebo-treated group. Tingling sensation was reported by 23 patients in the lamotrigine-treated group and by 21 in the placebo-treated group. Abnormal neurologic examination results, indicative of peripheral neuropathy (e.g., diminished ankle reflexes, sensory loss), were found in all patients. Nerve conduction tests were performed on nine subjects in each group and were positive in all cases. The baseline diabetes and pain data are presented in table 1.

Efficacy. Mean pain intensity gradually dropped from 6.4 $\pm$ 0.1 in the pretreatment week to 4.2 $\pm$ 0.1 during

Table 1 *Demographic and baseline diabetes pain data*

Characteristic	Lamotrigine, n = 27	Placebo, n = 26	*p* Value
Age, y	52.7 ± 2.1	57.8 ± 1.7	NS
Men/women	17/10	16/10	NS
Weight, kg	82.1 ± 2.3	81.4 ± 2.6	NS
Diabetes type			
Type 2	24	24	NS
Type 1	3	2	
Duration of diabetes	13.9 ± 1.7	9.6 ± 1.1	0.04
Fasting glucose, mg/dL	215 ± 15	196 ± 13	NS
Hemoglobin A1c, %	8.2 ± 0.3	8.4 ± 0.4	NS
Pain duration	3.6 ± 0.7	3.8 ± 0.6	NS
Previous treatment*			
Antidepressants	8	10	
Anticonvulsants	7	8	
Capsaicin cream	4	2	
Other	2	3	
Pain score, NPS	6.4 ± 0.1	6.6 ± 0.1	NS
MPQ			
Words	11.9 ± 0.7	11.4 ± 0.7	NS
Score	28.1 ± 2.0	29.6 ± 1.6	
PDI, total score	4.0 ± 0.6	4.6 ± 0.6	NS
BDI, total score	12.9 ± 1.5	16.1 ± 2.0	NS

Data expressed as mean ± SEM.

* Number of patients who have used each treatment for control of neuropathic pain.

MPQ = McGill Pain Questionnaire; PDI = Pain Disability Index; BDI = Beck Depression Inventory; NS = not significant; NPS = numerical pain scale.

treatment in the lamotrigine group, and from 6.5 ± 0.1 at pretreatment to 5.3 ± 0.1 during treatment in the placebo group (figure 1). The differences in mean pain intensities between the two groups were significant at lamotrigine doses of 200, 300, and 400 mg. The maximal reduction of pain from baseline was 37% in the lamotrigine-treated group, versus 20% in the control group. A 50% reduction in pain during the last 3 weeks of treatment was detected in 12 patients receiving lamotrigine and only in 5 receiving the placebo (*p* = 0.05).

Seven patients in the lamotrigine-treated group recorded daily intake of at least one tablet of an analgesic (a minimum of seven tablets/week) during the baseline phase, whereas only two were using a similar amount of rescue analgesics during the last 4 weeks of the treatment phase. In the placebo-treated group, only three required at least one tablet daily at baseline, but all three were still using the same amount at the end of the treatment phase.

The MPQ, BDI, and PDI scores did not change significantly from baseline to the end of the treatment phase in any of the groups (table 2). The global assessment of efficacy performed by the patients at the end of the treatment phase shows that seven of the 22 subjects (32%) in the lamotrigine-treated group regarded the drug as highly efficacious, nine (41%) regarded it as moderate, and six (27%) as low (figure 2). In the placebo-treated group, 2 of 21 subjects (10%) considered it as highly efficacious, 7 (33%) as moderate, and 12 (57%) as low (*p* = 0.07, chi-square). In contrast, 18 subjects in each group (lamotrigine, 81%; placebo, 86%) noted that the drug received was highly tolerable.

Adverse events. Seventeen adverse events were recorded in the lamotrigine-treated group and 21 in the placebo-treated group (table 3). Altogether, four patients were withdrawn from the study owing to adverse events, with two from each group. In the lamotrigine-treated group, rash developed in two patients during the fourth and the seventh weeks of the treatment period, both of which resolved shortly after lamotrigine use was discontinued. In the placebo-treated group, one subject had impo-
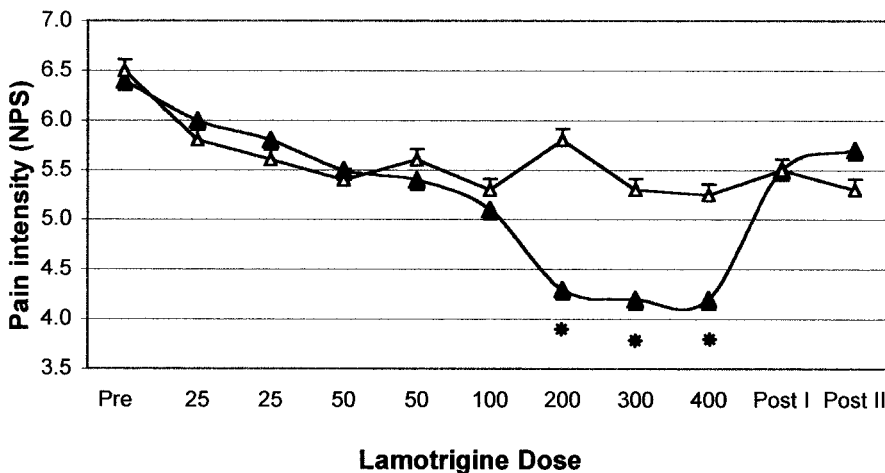
*Figure 1. Weekly pain intensity (mean ± SEM) in the lamotrigine-treated (dark labels) and in the placebo-treated (open labels) groups. *p < 0.001. Numbers in brackets represent the number of patients who were included in the analysis at each dose level. L = lamotrigine; P = placebo.*

Table 2 *Secondary and biochemical parameters*

Adverse event	Lamotrigine, n = 24		Placebo, n = 22		*p* Value
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	
MPQ, words	12.0 ± 0.8	12.5 ± 0.9	11.1 ± 0.8	10.7 ± 1.0	NS
BDI, total score	14.1 ± 1.5	14.5 ± 2.1	17.1 ± 2.2	15.9 ± 2.2	NS
PDI, total score	4.0 ± 0.8	3.8 ± 0.7	4.4 ± 0.9	4.3 ± 0.8	NS
Fasting glucose, mg/dL	212 ± 15	206 ± 13	185 ± 13	175 ± 17	NS
Hemoglobin A1c, %	8.4 ± 0.3	8.2 ± 0.3	8.4 ± 0.4	7.8 ± 0.4	NS

MPQ = McGill Pain Questionnaire; PDI = Pain Disability Index; BDI = Beck Depression Inventory; NS = not significant.

tence during the first week of treatment, and the other had diarrhea in the fifth week.

Discussion. The results of this study clearly show that lamotrigine attenuates painful diabetic neuropathy at a daily dosage of 200 to 400 mg, and has a significantly superior analgesic effect compared with placebo. The same range of lamotrigine dosages was suggested as efficacious in several other trials of diabetic neuropathy,[9] trigeminal neuralgia,[10] complex regional pain syndrome type 1,[11] chronic refractory neuropathic pain of mixed etiologies,[12] painful HIV-associated neuropathy,[13] and central poststroke pain.[14] Not all subjects in this study responded to treatment. Six patients regarded lamotrigine as having a low degree of efficacy, and can probably be categorized as "nonresponders." A similar group of nonresponding patients with painful diabetic neuropathy also was identified in a previous open-label trial.[9] A second category consists of nine patients who regarded lamotrigine as moderately effective. The third category consists of the seven patients who considered lamotrigine to be highly efficacious. It is possible that if insufficient analgesia has been achieved at a daily dose of 300 to 400 mg, increased titration of the dose still can be safe[21] and

effective. A superior analgesic effect of higher lamotrigine doses, however, has not been confirmed yet by controlled clinical trials.

The magnitude of pain relief achieved with lamotrigine in the current study is comparable with that found in recent studies with gabapentine[22] and tramadol.[23] In all three studies, the active drug reduced pain scores roughly by 40% to 45%, and the placebo by 15% to 20%. In addition, the adverse events profile of lamotrigine was similar to that of the placebo (with the exception of the two patients in whom rash developed). Lamotrigine therefore can be regarded as an effective and a safe agent for the treatment of painful diabetic neuropathy, provided it is slowly titrated.

The pathophysiologic process of neuropathic pain is not entirely clear. One of the suggested mechanisms for such pain is the generation of spontaneous activity in regenerating small-caliber primary afferents. Such activity has been shown in rat models of both nerve injury[1] and diabetes.[2] This activity requires the flow of sodium into the nerve. In addition, there now is evidence that by releasing excitatory amino acids, particularly glutamate, which, in turn, act at the NMDA receptor, the activity of small-caliber afferents may induce hyperexcitability in dorsal horn spinal neurons.[3,4] Lamotrigine inhibits the release of glutamate, possibly by stabilizing the neu-
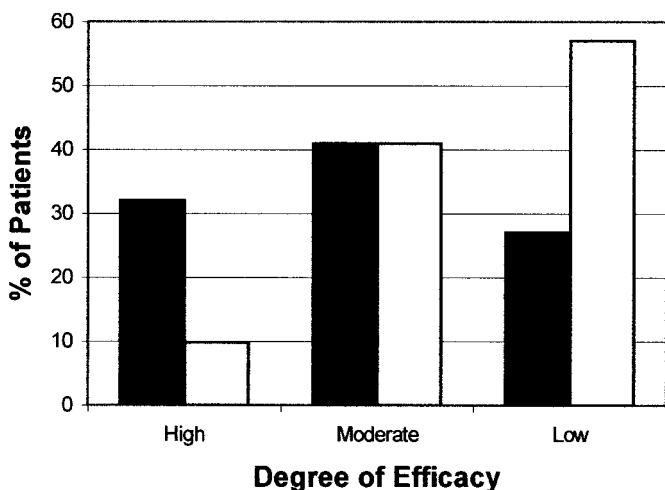
Figure 2. Global assessment of efficacy completed by patients at the end of the treatment phase. Data are presented as percentages of patients in each group. Dark bars represent lamotrigine-treated patients (n = 22), and open bars represent the placebo-treated group (n = 21).

Table 3 *Number of patients reporting adverse events*

Adverse event	Lamotrigine	Placebo
Rash	2	0
Nausea	4	4
Epigastric pain	3	1
Headache	2	2
Drowsiness	1	4
Dizziness	3	4
Other	2*†	6*‡§¶
Total	17	21

* Falling down.
† Constipation.
‡ Pancreatitis.
§ Impotence during first week of placebo treatment.
¶ Irritability.

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ral membrane through blocking activation of voltage-sensitive sodium channels.[6] It therefore is likely that the antinociceptive action of lamotrigine takes place at both peripheral (e.g., primary afferent) and central (e.g., spinal cord) levels. The unchanged glucose and HbA1C levels also indicate that lamotrigine analgesia is mediated by neural rather than biochemical mechanisms.

Recent reports suggest that lamotrigine may have mood-stabilizing action and antidepressant properties in patients with bipolar affective disorder.[24,25] The unchanged BDI scores in the lamotrigine-treated group indicate that lamotrigine exerts its analgesic effect independent of its mood-stabilizing effect. The lack of improvement in the MPQ and the PDI possibly can be attributed to the fact that most of the patients had long-lasting, intractable pain. The relatively short treatment period at an effective dose (practically, only 3 weeks) was too short to produce an improvement that would be reflected by those parameters. It is possible that a longer treatment period could lead to an improvement in those parameters as well.

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Relief of Painful Diabetic Peripheral Neuropathy With Pregabalin: A Randomized, Placebo-Controlled Trial

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Abstract: This was a 6-week, randomized, double-blind, multicenter study evaluating the efficacy of pregabalin in the treatment of painful diabetic neuropathy. Two hundred forty-six men and women with painful diabetic neuropathy received pregabalin (150 or 600 mg/day by mouth) or placebo. The primary efficacy variable was mean pain score at the end of treatment. Efficacy results indicate that pregabalin 600 mg/day significantly decreased mean pain score to 4.3 (vs 5.6 for placebo, P   .0002) and increased the proportion of patients who had a >50% decrease from baseline pain (39% vs 15% for placebo, P   .002). Pregabalin also significantly reduced sleep interference, past week and present pain intensity, sensory and affective pain scores, and bodily pain and decreased by >50% the number of patients describing their pain as gnawing, sickening, fearful, and punishing– cruel. More patients receiving pregabalin 600 mg/day than placebo showed improvement, as rated on the Clinical and Patient Global Impression of Change scales, 73% vs 45% and 85% vs 47%, respectively. Pregabalin 150 mg/day was essentially no different from placebo. Dizziness was the most common side effect. These study results show pregabalin 600 mg/day to be safe and effective in reducing the pain and other associated symptoms of painful diabetic neuropathy.

Perspective: *Painful diabetic peripheral neuropathy is a challenging neuropathic pain syndrome. This randomized controlled trial demonstrates that pregabalin, a new drug that interacts with the [2]- protein subunit of the voltage-gated calcium channel, is an efficacious and safe treatment for the pain of this condition.*

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Key words: *Pregabalin, neuropathic pain, diabetic neuropathy.*

Pregabalin is a selective, high-affinity ligand for the $\alpha_2\delta$- protein subunit of voltage-gated calcium channels,[12] which plays a role in development of pathologic changes believed to be associated with neuropathic pain in humans.[11,15] Pregabalin reduces calcium influx and diminishes release of several neurotransmitters.[5,9] It shows analgesic effects in animal models of neuropathic pain[8] and has analgesic[7,14] and antianxiety[22] effects in humans. This profile suggests pregabalin might be an effective new treatment for neuropathic pain.

The highly prevalent and heterogeneous neuropathies caused by diabetes are often complicated by pain.[3,10] Pharmacotherapy is the mainstay approach to treatment, and controlled studies have demonstrated potential effectiveness of opioid drugs,[13] varied antidepressants,[16,25] gabapentin,[2] tramadol,[24] and mexiletine.[21] Clinical responses vary, and treatment of painful diabetic neuropathy, like other neuropathic pains, continues to evolve. In this study, pregabalin was compared to placebo for its effect on pain and a variety of associated symptoms that commonly accompany diabetic neuropathy.

Materials and Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study in patients with diabetes and painful diabetic neuropathy. An Institutional Review Board or Ethics Committee for each of 29 participating US and Canadian centers approved the protocol, and each subject provided informed consent.

Patients were recruited between March 1998 and March 1999. Individuals with diabetes and painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years were potentially eligible to enter into the study. Neuropathy was confirmed by history and detailed neurologic examination. Inclusion criteria included age 18 years, hemoglobin A_{1C} levels 11%, and the ongoing experience of moderate to severe pain. Exclusion criteria included neurologic disorders unrelated to diabetic neuropathy, any condition that could confound study assess-
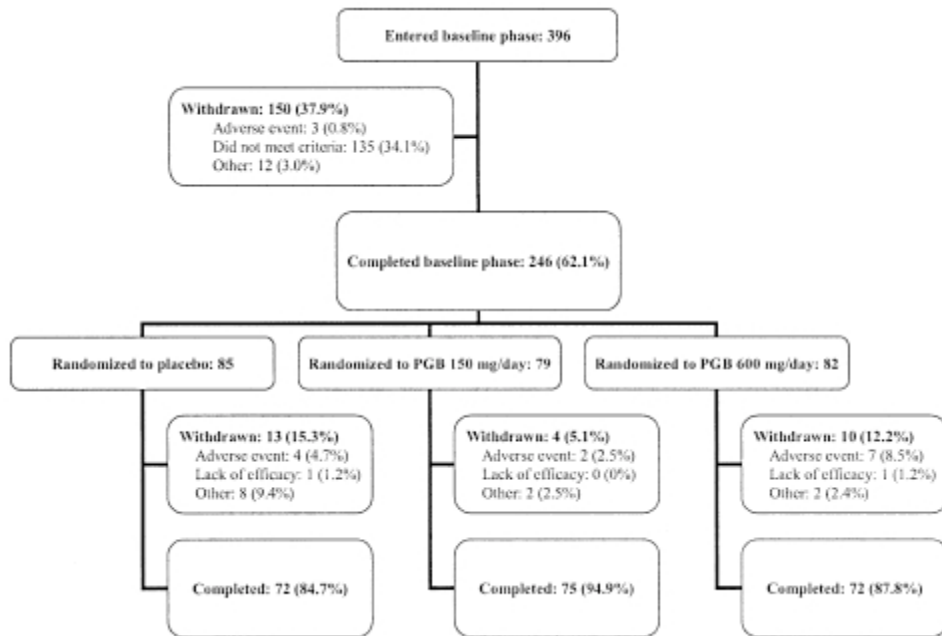
Figure 1. Patient disposition. Of 396 patients who entered the baseline period, 150 were withdrawn: 135 who did not meet study criteria, 3 who experienced AEs, and 12 others. Of those randomized to pregabalin 150 or 600 mg/day or placebo (N   246), 219 completed the 6-week study period. PGB, pregabalin.

ments, recent treatment with any investigational drug, or serious medical problems. Women could not be lactating and were required to have a negative pregnancy test result and to use appropriate contraception if of childbearing potential.

Eligible patients had to meet additional criteria for poorly controlled pain, including a score of   40 mm on the visual analog scale (VAS) of the Short Form-McGill Pain Questionnaire[20] (SF-MPQ) and an average daily pain score   4 for 4 or more days during baseline. Phenothiazines, antiarrhythmic agents, and pteridine and the combination of antihistamines and macrolide antibiotics were prohibited during the study owing to their proarrhythmic activity. Other medications that could affect efficacy or safety were to be discontinued either 14 days (antiepileptic drugs, nonsteroidal anti-inflammatory drugs) or 30 days (opioids, tricyclic antidepressants, benzodiazepines, muscle relaxants, capsaicin, mexiletine, dextromethorphan) before being administered study drug. Aspirin (for prophylaxis of myocardial infarction and transient ischemic attacks), acetaminophen (3 g/day), and stable doses of serotonin reuptake inhibitors were allowed.

Patients were randomly assigned to pregabalin (150 or 600 mg/day) or placebo. Randomization was computer-generated and conducted within sequential blocks of 6 patients. Eighty patients per treatment group was estimated to give 90% power to detect a difference of 1.3 in end point mean pain score between placebo and 600 mg/day pregabalin, assuming 2-sided testing at the 0.025 level.

After a 1-week baseline, eligible patients entered a 6-week (2-week titration/4-week fixed dose) double-blind treatment phase. The dose of pregabalin was ti-

trated from 25 mg/day to 150 mg/day or from 100 mg/day to 600 mg/day during the 2-week titration period and fixed thereafter. Pregabalin was provided as 2 differently sized capsules. To assure blinding, study medication was provided in 2 bottles, one with small-sized capsules containing 25 mg pregabalin or placebo and the other with large-sized capsules containing 100 mg pregabalin or placebo. Patients took 2 capsules from each bottle 3 times daily. At each stage of the study, including titration, all patients, regardless of treatment group, took the same number of capsules from each bottle per day. The blind was maintained until completion of study and data evaluability determination. Visits occurred at the start of baseline (week −1) and double-blind phases (week 0) and then biweekly (weeks 2, 4, and 6).

The primary efficacy parameter was pain. Each day on awakening, patients recorded their pain during the previous 24-hour period by circling the appropriate number on a numeric scale of 0 (no pain) to 10 (worst possible pain) in a daily diary. Secondary efficacy parameters assessed pain characteristics, sleep interference, health status, psychologic state, and global improvement. The SF-MPQ,[20] a well-validated multidimensional pain questionnaire, recorded past week pain intensity on a VAS ranging from 0 mm (no pain) to 100 mm (worst possible pain), present pain intensity (PPI) on a numeric scale of 0 (none) to 5 (excruciating), and past-week intensity of each of 11 sensory and 4 affective descriptors of pain on a numeric scale from 0 (none) to 3 (severe). The latter were summed to yield sensory and affective scores and added for total score. Sleep interference was recorded in daily diaries on a numeric scale of 0 (did not interfere with sleep) to 10 (completely interfered, unable to sleep because of pain). The 36-Item Short-form Health Sur-

Table 1. Baseline Demographic and Disease Characteristics

| | | PREGABALIN | |
CHARACTERISTIC	PLACEBO (n 85)	150 MG/DAY (n 79)	600 MG/DAY (n 82)
Men/women, N	46/39	57/22	46/36
White/black/hispanic/other, N	67/7/8/3	74/3/2/0	65/9/8/0
Age (y), mean SD	57.1 10.3	56.3 9.4	57.8 9.5
Weight (kg), mean SD	90.81 20.40	97.96 18.37	96.55 19.77
Diabetes characteristics			
Type 1, N	14 (16.5%)	7 (8.9%)	2 (2.4%)
Type 2, N	71 (83.5%)	72 (91.1%)	80 (97.6%)
HbA$_{1c}$ values, mean SD	8.1 1.4	8.2 1.5	8.2 1.4
Duration (y), mean SD	10.6 8.3	8.2 9.1	9.3 8.8
Distribution of neuropathic pain			
Lower extremities, N	85 (100%)	79 (100%)	82 (100%)
Upper extremities, N	30 (35.3%)	28 (35.4%)	26 (31.7%)
Antidiabetic medication, N	81 (95.3%)	74 (94.9%)	77 (93.9%)

Abbreviation: SD, standard deviation.

vey[27] (SF-36), a commonly used measure of health status, and Profile of Mood States[17] (POMS), a well-validated measure of psychologic state, were administered at week 0 and the final visit. Clinician and Patient Global Impression of Change (CGIC, PGIC) were each scored from 1 (very much improved) to 7 (very much worse) at the final visit.

Safety was evaluated by adverse events (AEs); clinical laboratory determinations; electrocardiogram; and general medical, neurologic, and ophthalmologic examinations. The neurologic examination included a clinician-rated question assessing the presence or absence of allodynia. Changes from baseline to the end of the double-blind phase in examination data were recorded as AEs if they were deemed clinically significant by the investigators.

Plasma pregabalin concentrations from blood collected at weeks 0, 2, 4, and 6 were determined by using a validated high-performance liquid chromatographic method with ultraviolet detection. Predicted (based on a pharmacokinetic model of pregabalin constructed from data rich [serial plasma collections] single- and multiple-dose studies in healthy volunteers, including a single-dose tolerance and pharmacokinetic study, 2 multiple-dose tolerance and pharmacokinetic studies, and a single-dose, food-effects study) versus observed pharmacokinetic values were analyzed by using nonlinear mixed effects modeling (NONMEM Version V; University of California at San Francisco, San Francisco, Calif).

Analyses were conducted on the intent-to-treat population (all randomized patients who received at least one dose of study medication). Analysis of covariance main effects models, with baseline as covariate and 95% confidence intervals (CIs), were constructed on the difference in least square (LS) means between each of the two dosages of pregabalin and placebo to evaluate group differences in pain scores from daily pain diaries, SF-MPQ scores, sleep interference scores, POMS scales, and scores on the SF-36 domains. Generalizability of results among centers was tested by repeating the analysis, including a treatment-by-center interaction term. PGIC, CGIC, and the proportion of patients with at least a 50% reduction in mean pain score (baseline to end point) were analyzed by using the Cochran-Mantel-Haenszel test. Patients with missing data for a given parameter at baseline or at the time point to be analyzed were automatically excluded from that analysis.

Results

Patient disposition is shown in Fig 1, and demographic and baseline characteristics are summarized in Table 1.

At end point, patients receiving 600 mg/day pregabalin had a significantly lower mean pain score than did patients receiving placebo (P .0002) (Table 2), and significantly more had a 50% reduction from baseline pain (P .002) (Fig 2). Starting at week 2, when they were receiving the full 600 mg/day dosage of pregabalin, these patients had significantly greater weekly decreases from baseline mean pain scores (P .05 vs placebo) (Fig 3).

VAS, PPI, sensory, affective, and total scores on the SF-MPQ were all significantly lower after treatment with 600 mg/day pregabalin (P .01 vs placebo) (Table 3). The percentage of patients who reported gnawing, sickening, fearful, and punishing-cruel pain was more than halved. Decreases from baseline VAS, PPI, and total scores were greater starting at week 2, the first assessment of these parameters during the treatment phase (P .05 vs placebo).

Patients receiving 600 mg/day pregabalin had significantly lower sleep interference scores starting at week 1 (Fig 3) and at end point (least square mean difference, 1.152; 95% CI, 1.752 to 0.551; P .0004 vs placebo). These patients also had significantly better CGIC and PGIC assessments (P .002 for either vs placebo), and more were rated as improved (Fig 4).
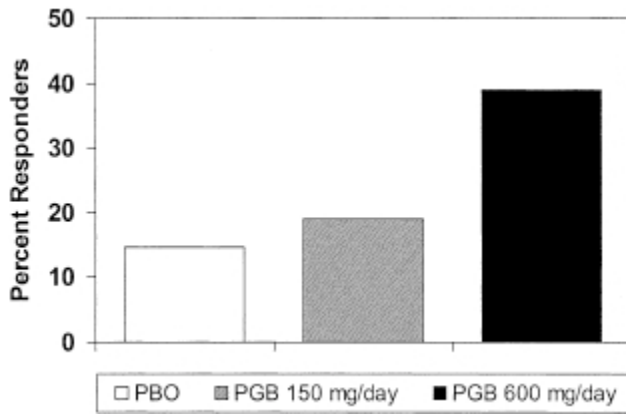
Figure 2. Percentage of patients responding to treatment with a ≥50% decrease in baseline daily pain. Decrease in pain was significantly greater for those who received 600 mg/day pregabalin compared with those who received placebo (*P* = .002). PGB, pregabalin; PBO, placebo.

There were no treatment-related differences in mood assessed by the POMS or in health status assessed by the SF-36, except for bodily pain, which was significantly improved by both doses of pregabalin (*P* = .0106 for either dose vs placebo). Pregabalin 150 mg/day was not significantly different from placebo on any other efficacy parameter.

There were no clinically significant changes in deep tendon reflexes or peripheral sensory examination (pin prick, vibration perception) among treatment groups, but among patients with allodynia at baseline, most no longer reported allodynia after pregabalin (18/28 [64.3%] 600-mg/day and 13/23 [56.5%] 150-mg/day vs 5/22 [22.7%] placebo).

A summary of treatment-associated and not-associated AEs by decreasing frequency appears in Table 4. The most common treatment-associated AEs in the 600-mg/day group were dizziness (30.5% of patients), somnolence (18.3% of patients), and headache (13.4%), whereas in the 150-mg/day group, the most common AEs were dizziness (6.3%), somnolence (5.1%), and asthenia (3.8%). In the placebo group, headache (7.1%) and somnolence, asthenia, and amblyopia (3.5% each) were the most commonly observed treatment-associated AEs. Most AEs were of a maximum intensity of mild or moderate. AEs considered severe that occurred in more than 1 patient in the 600-mg/day group were dizziness (3 patients), somnolence (2 patients), and asthenia (2 patients). No AEs considered severe were reported by more than 1 patient in the 150-mg/day pregabalin group. Together, dizziness, somnolence, and headache caused 9 patients to discontinue the study (6 pregabalin 600-mg/day, 1 pregabalin 150-mg/day, 2 placebo). There were no clinically significant differences among treatment groups in ophthalmologic examinations, physical examination parameters, including orthostatic hypotension and electrocardiogram, and no evidence of worsening glucose control or diabetic ketoacidosis.

Steady-state plasma pregabalin concentrations associated with 150 and 600 mg/day ranged from 0.141 to 3.53
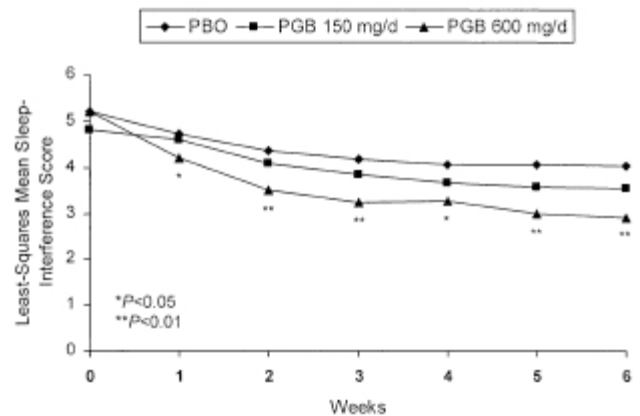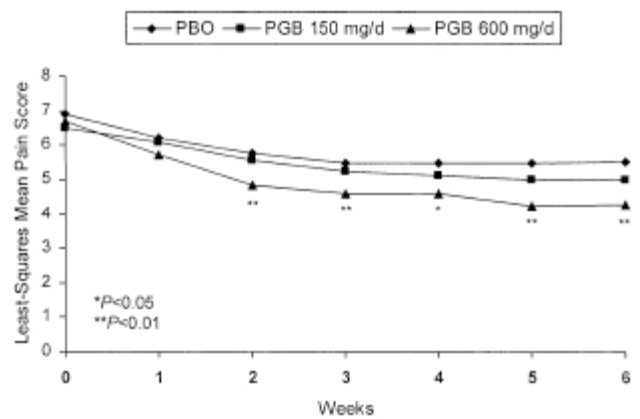
Figure 3. Reduction in mean pain score (top panel) and in mean sleep-interference score (bottom panel) over time assessed by daily pain and by daily sleep diaries. PGB, pregabalin; PBO, placebo.

g/mL and from 0.174 to 17.6 g/mL, respectively. There was a linear relationship between predicted and observed values (Fig 5).

Discussion

Painful neuropathy is highly prevalent in the diabetic population and can profoundly undermine quality of life.[10] Pain management is an essential component in the comprehensive care of these patients.

Several controlled studies have demonstrated that painful diabetic peripheral neuropathy can be relieved by antidepressants,[19] anticonvulsants,[18] tramadol,[24] agonist opioids,[28] and topical application of capsaicin,[29] and recent meta-analyses[4,26] support those findings. Unfortunately, the use of these agents can be limited by the extent of pain relief provided and the occurrence of significant side effects. Thus, a need exists for additional safe and effective agents for painful diabetic peripheral neuropathy.

In this study, patients who received pregabalin 600 mg/day experienced significantly less pain than those who received placebo. The average reduction in pain score from baseline was 2.4 on a 0 to 10 numeric scale,

Table 2. **Daily Pain**

| | | MEAN | SD PAIN SCORE | | | LS MEAN | | LS MEAN DIFFERENCE | | |
| | | | END | | | SE | | (95% CI) | | P |
TREATMENT	N	BASELINE		POINT		END POINT		PREGABALIN-PLACEBO		VALUE
Placebo	82*	6.9	1.6	5.8	2.2	5.55	0.23			
Pregabalin										
150 mg/day	79	6.5	1.3	4.9	2.2	5.11	0.24	0.440 (	1.080 to 0.199)	.1763
600 mg/day	82	6.7	1.7	4.3	2.7	4.29	0.26	1.264 (	1.890 to 0.639)	.0002

Abbreviations: SD, standard deviation; LS, least square; SE, standard error; CI, confidence interval.
*85 at baseline.

with 39% of patients having 50% reduction in their pain. This degree of response is widely considered to be clinically meaningful and corresponds with the highest degree of improvement assessed by PGIC.[6,7]

Treatment with pregabalin at 600 mg/day also reduced sleep interference and significantly improved all components of the SF-MPQ by week 2. A lower prevalence of allodynia, improvement in bodily pain, and substantial global improvement were observed at study's end. Pregabalin showed predictable pharmacokinetics and was well tolerated, as evidenced by the low rates of study discontinuation.

Although direct comparisons of pregabalin with tricyclic antidepressants and gabapentin have not been conducted, the findings in this study suggest that pregabalin produces clinically significant improvement in the range observed with these other drugs. Pregabalin is structurally and mechanistically related to gabapentin but differs from gabapentin in exhibiting linear pharmacoki-

netics with increasing dose and low intersubject variability. These properties might make pregabalin easier to prescribe and might impart a better-defined effective dose range.

In another controlled trial, pregabalin 300 mg/day also significantly improved pain, sleep interference, and mood in patients with painful diabetic neuropathy.[23] Together, these 2 independent, randomized clinical trials constitute evidence that pregabalin at 300 or 600 mg/day produces significant improvement of pain, sleep, and at least some aspects of health status and mood. Consistent with clinically recognized, dose-dependent effects of anticonvulsants in neuropathic pain, best characterized with gabapentin,[1] pregabalin 150 mg/day did not differ from placebo.

Despite substantial advances in pharmacotherapy of neuropathic pain, outcomes are often unsatisfactory. Many drugs are tried despite a lack of evidence for safety or efficacy in the diabetic population, emphasizing the need for controlled clinical trials of new pharmacother-

Table 3. **Short-Form McGill Pain Questionnaire Scores**

SCORE	TREATMENT	N	LS MEAN END POINT	SE	LS MEAN DIFFERENCE (95% CI) PREGABALIN-PLACEBO		P VALUE
VAS	Placebo	82	58.05	2.68			
	Pregabalin						
	150 mg/day	79	53.27	2.75	4.78 (	12.20 to 2.64)	.2058
	600 mg/day	82	43.38	2.70	14.67 (	21.92 to 7.41)	.0002
PPI	Placebo	82	1.96	0.11			
	Pregabalin						
	150 mg/day	79	1.78	0.12	0.17 (	0.49 to 0.14)	.2836
	600 mg/day	82	1.30	0.12	0.66 (	0.97 to 0.35)	.0002
Sensory	Placebo	82	14.61	0.73			
	Pregabalin						
	150 mg/day	79	12.65	0.76	1.97 (	3.99 to 0.06)	.0570
	600 mg/day	82	10.07	0.74	4.54 (	6.53 to 2.56)	.0002
Affective	Placebo	82	3.35	0.29			
	Pregabalin						
	150 mg/day	79	2.78	0.30	0.57 (	1.38 to 0.24)	.1664
	600 mg/day	82	2.04	0.30	1.31 (	2.10 to 0.51)	.0028
Total	Placebo	82	17.97	0.96			
	Pregabalin						
	150 mg/day	79	15.48	0.99	2.49 (	5.14 to 0.16)	.0651
	600 mg/day	82	12.14	0.97	5.83 (	8.43 to 3.23)	.0002

Abbreviations: LS, least square; SE, standard error; CI, confidence interval; VAS, visual analog scale; PPI, present pain intensity.

CGIC

Pregabalin 600 mg/day vs placebo comparison significant, *P=0.002*, using the CMH test.

PGIC

Pregabalin 600 mg/day vs placebo comparison significant, *P=0.002*, using the CMH test
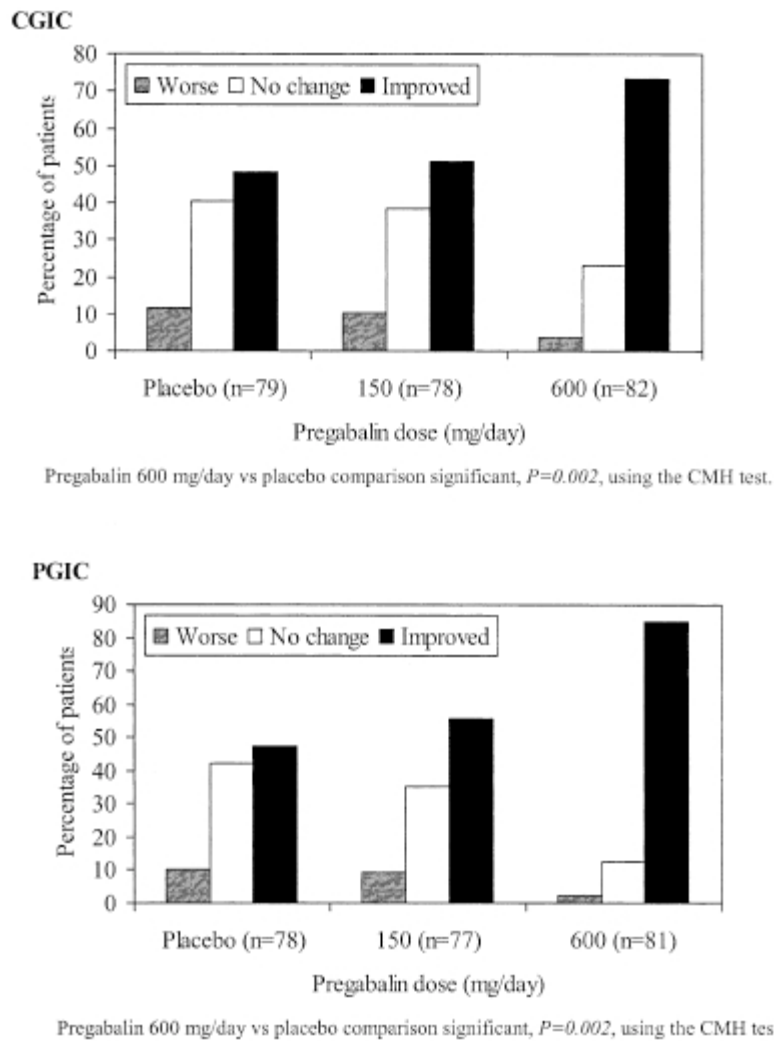
Figure 4. CGIC and PGIC scores at study end point. A significantly greater percentage of patients who received pregabalin 600 mg/day vs placebo had improved scores on both scales (*P*   .002). CMH, Cochran-Mantel-Haenszel.

apies to expand treatment options and further the goal of evidence-based decision making. The present, 6-week study establishes that pregabalin 600 mg/day is safe and effective in patients with painful diabetic neuropathy. Although no conclusions about the durability of response or AE profile during long-term administration can be drawn from this study, 75 patients (91%) treated with 600 mg/day pregabalin and 73 patients (92%) treated with pregabalin 150 mg/day entered the open-label extension, and 73 patients (86%) treated with placebo were converted to pregabalin treatment for the open-label extension. Additional studies are needed to further explore dose response at higher doses, provide comparative efficacy data against other treatments, assess value of combination therapies, and confirm long-term treatment effectiveness.

Statement of Contributions

Drs Ralph Richter and Russell Portenoy participated as investigators in this multicenter study. Drs Richter and

Table 4. Adverse Events

	% PATIENTS		
		PREGABALIN	
ADVERSE EVENT	PLACEBO (n 85)	150 MG/ DAY (n 79)	600 MG/ DAY (n 82)
Dizziness	2.4	10.1	37.8
Somnolence	3.5	5.1	22.0
Peripheral edema	4.7	3.8	17.1
Headache	10.6	7.6	15.9
Asthenia	3.5	3.8	12.2
Accidental injury	5.9	2.5	9.8
Weight gain	0	1.3	9.8
Amblyopia	5.9	2.5	8.5
Dry mouth	2.4	0	8.5
Pain	8.2	3.8	7.3
Constipation	4.7	3.8	6.1
Infection	9.4	12.7	6.1
Diarrhea	3.5	5.1	2.4

Figure 5. Predicted vs observed steady-state plasma pregabalin concentrations. Values for 150 mg/day and 600 mg/day ranged from 0.141 to 3.53 g/mL and 0.174 to 17.6 g/mL, respectively.

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BJA

Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy

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Editor's key points

- Tapentadol is a μ-opioid agonist and also inhibits norepinephrine reuptake.
- This study evaluates the main analgesic mechanisms of tapentadol in diabetic neuropathy.
- Conditioned pain modulation and offset analgesia were used to investigate the endogenous pain pathways.
- Tapentadol's analgesic effect in diabetic neuropathy is mainly via activation of descending inhibitory pathways.

Background. Tapentadol is an analgesic agent for treatment of acute and chronic pain that activates the μ-opioid receptor combined with inhibition of neuronal norepinephrine reuptake. Both mechanisms are implicated in activation of descending inhibitory pain pathways. In this study, we investigated the influence of tapentadol on conditioned pain modulation (CPM, an experimental measure of endogenous pain inhibition that gates incoming pain signals as a consequence of a preceding tonic painful stimulus) and offset analgesia (OA, a test in which a disproportionally large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation).

Methods. Twenty-four patients with diabetic polyneuropathy (DPN) were randomized to receive daily treatment with tapentadol sustained-release (SR) [average daily dose 433 (31) mg] or placebo for 4 weeks. CPM and OA were measured before and on the last day of treatment.

Results. Before treatment, none of the patients had significant CPM or OA responses. At week 4 of treatment, CPM was significantly activated by tapentadol SR and coincided with significant analgesic responses. CPM increased from 9.1 (5.4)% (baseline) to 14.3 (7.2)% (placebo) and 24.2 (7.7)% (tapentadol SR, $P<0.001$ *vs* placebo); relief of DPN pain was also greater in patients treated with tapentadol than placebo ($P=0.028$). Neither placebo nor tapentadol SR treatment had an effect on the magnitude of the OA responses ($P=0.78$).

Conclusions. Tapentadol's analgesic effect in chronic pain patients with DPN is dependent on activation of descending inhibitory pain pathways as observed by CPM responses.

Clinical trial registration. The study was registered at trialregister.nl under number NTR2716.

Keywords: chronic pain, diabetic polyneuropathy; conditioned pain modulation; morphine; neuropathic pain, offset analgesia; pain, tapentadol

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Endogenous pain modulatory pathways are important regulators of human pain perception. Both inhibitory and facilitatory descending pathways, originating at higher centres, modulate the activity of nociceptive neurones at the level of the spinal dorsal horn, enhancing or inhibiting noxious signal propagation to the brain.[1] A shift in the balance between pain inhibition and facilitation has been suggested to underlie the development or maintenance of many chronic pain syndromes, such as fibromyalgia, irritable bowel syndrome, chronic pancreatitis, and neuropathic pain syndromes.[2–5] Animal studies show that effective engagement of descending inhibition protects against chronic neuropathic pain development. Various neurotransmitter systems are involved in the descending pain pathways, including endogenous opioid peptides, norepinephrine, and serotonin. Release of endogenous opioids and norepinephrine underlie pain inhibition, whereas the serotonergic

pathway has both pain inhibitory and facilitatory properties.[6–8] The new analgesic tapentadol is a centrally acting drug with a combined mechanism of action. Tapentadol is a μ-opioid receptor (MOR) agonist (its affinity for the MOR is 50 times less than that of morphine) and inhibits neuronal reuptake of norepinephrine.[6 9] Both mechanisms act synergistically to produce analgesia.[10] Animal studies indicate that the opioidergic component is more important in the treatment of acute pain, whereas the noradrenergic component is largely involved in the treatment of chronic neuropathic pain.[8]

As tapentadol modulates opioidergic and noradrenergic pathways simultaneously, the analgesic effect of tapentadol is thought to rely on the enhancement of descending pain inhibitory activity.[11] However, up to now, no studies have been conducted to confirm the presence of such an effect in humans. In the current study, the effects of tapentadol on

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two experimental paradigms, conditioned pain modulation (CPM) and offset analgesia (OA), were tested in chronic pain patients with diabetic polyneuropathy (DPN). CPM is an experimental measure of endogenous pain modulation that gates incoming pain signalling as a consequence of a preceding or simultaneous tonic painful stimulation.[12–17] OA is a test in which a disproportionally large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation.[18 19] Both tests have been used previously to evaluate the engagement of pain modulatory pathways.[4 14 19]

We performed a randomized, parallel-design, placebo-controlled study in chronic pain patients with DPN on the effect of a 4-week tapentadol treatment on CPM, OA, and pain relief. We hypothesize that tapentadol's analgesic efficacy relies, in part, on the engagement of endogenous pain inhibitory pathways.

Methods

Chronic pain patients were recruited to participate in the study performed at the Leiden University Medical Center over the period January 2012–October 2012, after approval of the protocol was obtained from the local Medical Ethics Committee and the Central Committee on Research involving Human Subjects (CCMO, The Hague, The Netherlands). The study was registered at trialregister.nl under number NTR2716 and has EudraCT number 2010-012175-26. The study was registered as an addendum to an earlier trial on the effects of a single dose of tapentadol and morphine on CPM. All participants gave written informed consent and underwent a physical examination before enrolment in the study.

Patients were recruited via an advertisement in the journal of the national diabetic society. All recruited patients had diabetes and chronic pain in hands and/or legs and feet. They were included in the study when they were 18–75 yr, had a BMI below ≤ 40 kg m^{-2}, and had: (i) presence of at least two of the following symptoms in legs, arms, or both (in a stocking-glove distribution): (a) symmetrical dysesthesias or paresthesias, (b) burning or painful feet with nighttime worsening, or (c) peripheral tactile allodynia; and (ii) an abnormal warm or cold detection threshold, an abnormal warm or cold pain threshold, or allodynia observed with quantitative sensory testing (QST). Exclusion criteria included: indication of the presence of severe medical diseases (e.g. liver function elevation); allergy to opioids; current use of benzodiazepines and/or other sedatives; present or past use of illicit/recreational substances; present or past alcohol abuse; history of mental illness or epilepsy; pregnancy and/or lactation; current use of strong opioids; and inability to understand the purpose and instructions of the study. The patients were allowed to continue the following pain medications as long as they used a constant dose for the 8 weeks before the study and the dosage could be kept constant during the whole study period: acetaminophen, non-steroidal anti-inflammatory drugs, amitriptyline, gabapentin, and pregabalin. Patients who had been using opioids previously (and terminated treatment due to the absence of efficacy or side-effects) were eligible for inclusion.

Study design

This randomized, double-blind, placebo-controlled study was performed in 24 DPN patients (see Consort flow chart, Fig. 1).

Fig 1 Consort study flow chart.
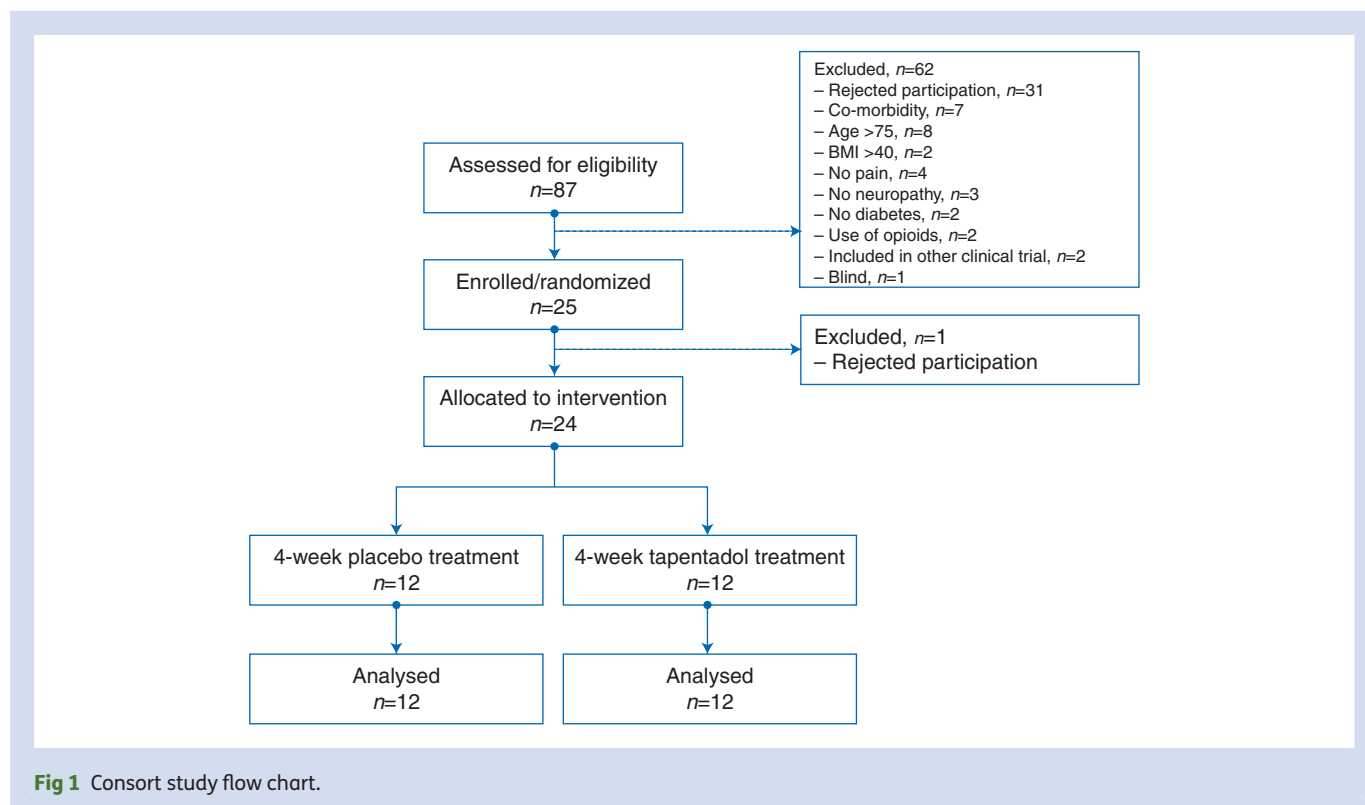
Twelve patients were treated orally for 4 weeks with tapentadol slow release (SR), 12 others with placebo. The dose of tapentadol SR was titrated to effect starting with 100 mg twice daily in week 1, followed by 200 mg twice daily in week 2, and 250 mg twice daily in weeks 3 and 4. In the case of the presence of side-effects unacceptable to the patient, the tapentadol dose was decreased to a dose where side-effects were absent or acceptable. All patients were tested twice, once 1 day before the treatment period and once on the last day of treatment. On each study day, the subjects were familiarized with the test procedures. Next, the CPM and OA responses were obtained. Spontaneous pain scores [using an 11-point numerical rating scale (NRS) from 0 (corresponding with no pain) to 10 (corresponding with most imaginable pain)] and side-effects [presence of nausea, vomiting, drowsiness, dizziness, and dry mouth, using a dichotomous scale (yes/no)] were monitored on a weekly basis.

To get an indication of the nerve-fibre involvement in the patient population, QST was performed according to the standardized protocol of the German Research Network on Neuropathic Pain.[20] In short, this protocol assesses cold, heat, and mechanical detection and pain thresholds; paradoxical heat sensations; mechanical pain sensitivity; allodynia; wind-up and vibration; and pressure pain thresholds. Sensory testing was performed on the hand and foot of all pain patients included in the study.

Application of nociceptive stimuli for CPM and OA testing

Heat pain was induced on the lower part of the non-dominant arm with a 3×3 cm thermal probe connected to the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). The probe was calibrated according to the specifications of the manufacturer. During the heat pain stimulation, subjects continuously quantified the pain intensity level of the stimulus using a slider on a computerized potentiometer that ranged from 0 (no pain) to 100 (worst pain imaginable). This allowed for continuous monitoring of the visual analogue scale (eVAS). To overcome sensitization, the thermode was moved between different zones on the forearm and ample time was incorporated between the different heat stimuli. On each of the two study days (i.e. before treatment and at 4 weeks of treatment), the individual test temperature was determined by applying a series of heat stimuli. First, the temperature was increased from 32°C (baseline temperature) by 1.5°C s^{-1} to a target temperature of 42°C and kept constant for 10 s. If the eVAS was <50 mm, a next test was performed increasing the target temperature in steps of 1°C. The cut-off temperature for these series was 49°C. The temperature evoking an eVAS of at least 50 mm was used during the remainder of the study.

Cold pain was induced using a cold-water reservoir produced by a rapid water-cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands). The subject's foot and lower leg was immersed into the cold water reservoir, which could be set at different temperatures ranging from 6°C to 18°C. The temperature that produced an eVAS of at least 30 mm was

used in the remainder of the study. After the exposure to cold water, the subject's extremity was warmed to normal temperature using warm water collected from the counter-current outlet of the IcyDip system.

CPM and OA

The method to induce CPM has been published previously.[2 4 14] In short, to measure CPM, two series of three pain tests were performed. One series included stimulation of the forearm with the experimental stimulus (heat pain). For this, the temperature of the heat probe gradually increased from baseline temperature (32°C) to the earlier set test temperature (at 1.5°C s^{-1}) and remained constant for 30 s. Next, the temperature rapidly returned (at 6°C s^{-1}) to baseline. The second series included stimulation with both the experimental stimulus and the conditioning stimulus (CS) (cold pain). The CS was applied 25 s before the start of the experimental stimulus and ended simultaneously with the end of the experimental stimulus. In both sessions, the subjects only rated the pain intensity level of the experimental stimulus (heat pain on the arm). There were 3 min intervals between single tests.

OA was studied by applying a three-temperature paradigm as described by Grill and Coghill.[18] The temperature was ramped at 1.5°C s^{-1} from baseline temperature to the previously set test temperature. The test temperature was kept constant for 5 s after which it was raised by 1°C for 5 s and next decreased by 1°C for 20 s. At the end of the test, the temperature quickly returned (6°C s^{-1}) to baseline. This temperature paradigm was applied three times with a 3-min interval between tests.

Randomization and blinding

Randomization and allocation was performed by the local pharmacy using a computer-generated randomization list. Placebo tablets were fabricated by the pharmacy and were identical to the tapentadol tablets in form, size, and taste. The tablets were repackaged into unmarked containers and delivered to the research team and subsequently by the research team to the patients. The research team remained blinded to treatment until all CPM and OA responses had been analysed.

Data analyses

To quantify the magnitude of CPM, the peak eVAS scores were used in the analyses. For each subject, the average peak eVAS without and with CS were calculated. Next, relative CPM responses were calculated to correct for variations in peak response between sessions and subjects using the formula:[2 21 22] [(mean eVAS without CS stimulus–mean eVAS with CS)/ (mean eVAS without CS)]$\times$100%.

OA responses were quantified as previously described.[14 19] In short, the decrease in eVAS from the peak eVAS value to the eVAS nadir after the 1°C decrease in the test stimulus was measured (ΔeVAS) and corrected for the value of the peak eVAS: ΔeVAS$_C$=[ΔeVAS/(peak eVAS)]$\times$100%.

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Sample size and statistical analysis

A sample size of 24 (12 per treatment level) was calculated by assuming an increase in CPM of 20% (15%) [mean (SD)] with $\alpha=0.05$ and $\beta>0.95$. An effect of 20% was chosen as this constitutes the 'average' value of CPM in healthy volunteers and is probably the maximum magnitude of CPM attainable in humans.[14]

The effect of the CS on the relative eVAS responses was tested by two-tailed paired t-test. Treatment effects were assessed by two-way repeated-measures analysis of variance (factors: time and treatment). For all analyses, the software package SigmaPlot version 12.5 for Windows (Systat Software Inc., San Jose, CA, USA) was used. Data are presented as mean (SEM) unless otherwise stated and P-values of <0.05 were considered significant.

Results

Eighty-seven patients responded to the advertisement (Fig. 1). Thirty-one decided not to participate after they were informed on the nature of the study. Thirty-one others were excluded because of the absence of pain, diabetes, or neuropathy (as assessed by QST), not meeting age- or BMI-related inclusion criteria, the use of strong opioids, or their inclusion in another trial. Twenty-five subjects were enrolled in the study and randomized. One patient retracted her consent after randomization; she was replaced by another subject. The patient characteristics of the participating patients are given in Table 1. All patients completed the study without major side-effects. QST measurements obtained from affected hands and feet are presented in Figure 2. The patients presented with a mixed small and large fibre neuropathy as evidenced

Table 1 Patient characteristics

	Tapentadol	Placebo
Men/women (n)	7/5	7/5
Age [yr; median (range)]	63 (58–67)	64 (57–66)
Weight [kg; median (range)]	95 (56–140)	97 (71–125)
Height [cm; median (range)]	177.5 (169–196)	178 (168–194)
Duration of disease		
Diabetes mellitus [yr; median(range)]	12 (3–35)	11 (2–45)
Neuropathic pain [yr; median (range)]	6 (1–10)	6.5 (2–25)
Affected limbs		
Legs (n)	8	8
Legs+arms (n)	4	4
Medication		
Insulin	8	6
Metformin	11	7
Pregabalin	3	2
Duloxetin	2	0
Amitriptyline	1	1
Steroid	0	2
Paracetamol	1	1

Fig 2 Results of the QSTs obtained on the affected skin areas (hand/feet). The data are the populations mean z-scores (SEM). z-Scores were calculated in relation to a population of healthy subjects as determined by Rolke and colleagues.[20] z-Values above the broken line indicate a gain of function, whereas values below this line are indicative for a loss of sensory function. CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; PHS, paradoxal heat sensations; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; ALL, dynamic mechanical allodynia; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

by reduced cold and warm detection thresholds and paradoxical heat sensation (signs of small fibre involvement) and a reduced vibration detection threshold (on the feet more than on the hands; a sign of large fibre involvement). Importantly, allodynia was observed in seven (of 24) patients. During the study period, the daily drug dose was titrated to a level with sufficient analgesic effect and acceptable side-effects to the patients. In the placebo group, the maximum daily dose of 500 mg day^{-1} was reached in all subjects compared with an average of 433 (31) mg day^{-1} in the tapentadol SR group.
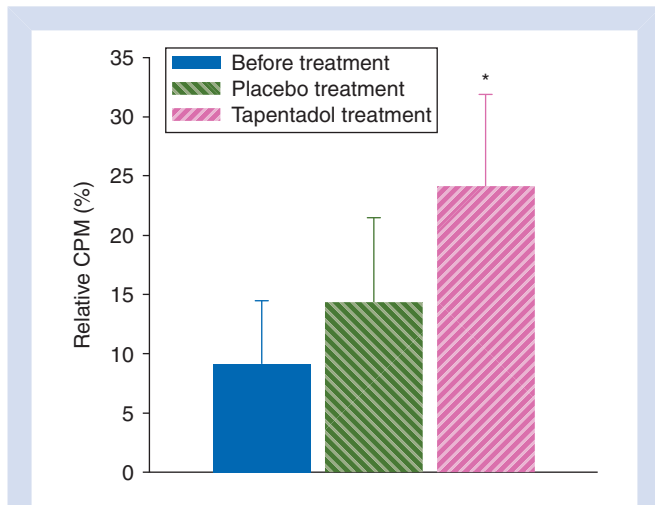
Fig 3 Relative CPM responses at baseline (before treatment), in patients receiving a 4-week placebo treatment, and patients receiving a 4-week tapentadol treatment. At baseline, the effect of the CS was not significant ($P=0.09$). During placebo and tapentadol treatment, the effect of the CS was significant (placebo $P=0.04$, tapentadol $P<0.01$). A treatment effect was present with greater increase in CPM responses during tapentadol treatment than during placebo treatment (*$P<0.001$ *vs* placebo).

Reported side-effects were nausea (placebo: $n=4$; tapentadol: $n=3$), vomiting (placebo: $n=0$; tapentadol: $n=2$), sedation (placebo: $n=2$; tapentadol: $n=6$), dizziness (placebo: $n=2$; tapentadol: $n=6$), and dry mouth (placebo: $n=1$; tapentadol: $n=5$).

Before treatment, significant CPM responses were not detectable as the effect of the CS was not significant [CPM=9.1 (5.4)%, $P=0.09$, Fig. 3]. After both treatments, CPM responses increased to significant levels [placebo: CPM=14.3 (7.2)%, $P=0.04$; tapentadol SR: CPM=24.2 (7.7)%, $P<0.01$]. A clear treatment effect was present with tapentadol SR CPM responses greater than placebo responses ($P<0.001$, Fig. 3).

Weekly pain scores after tapentadol and placebo treatments are given in Figure 4A. It shows a clear distinction in pain reduction in weeks 3 and 4 of treatment with greater analgesia in patients treated with tapentadol SR [pain scores at baseline 6.5 (0.6) reduced to 4.8 (0.7) after placebo and 3.9 (0.6) after tapentadol; 4-week treatment effect, $P=0.03$]. Plotting pain relief *vs* CPM responses shows that greater pain relief from tapentadol SR coincided with enhanced CPM responses (Fig. 4B).

OA responses before tapentadol treatment and at week 4 of treatment are given in Figure 5. As contrast, an example of an OA response in age- and sex-matched healthy volunteer is added in Figure 5A (data from Niesters and colleagues).[19] ΔeVAS values in healthy volunteers in the age cohort 40–80 years range between 90% and 100%, irrespective of sex.[19] Before treatment, ΔeVAS was 40.7 (7.4)%. Neither placebo [change from baseline +2.6 (11.6)%] nor tapentadol SR treatment [change from baseline −0.8 (3.7)%] had an effect in the magnitude of OA (treatment effect, $P=0.78$).

Discussion

Tapentadol is a new centrally acting analgesic agent for treatment of acute and chronic pain,[11 23–26] which acts through MOR agonism and neuronal norepinephrine reuptake
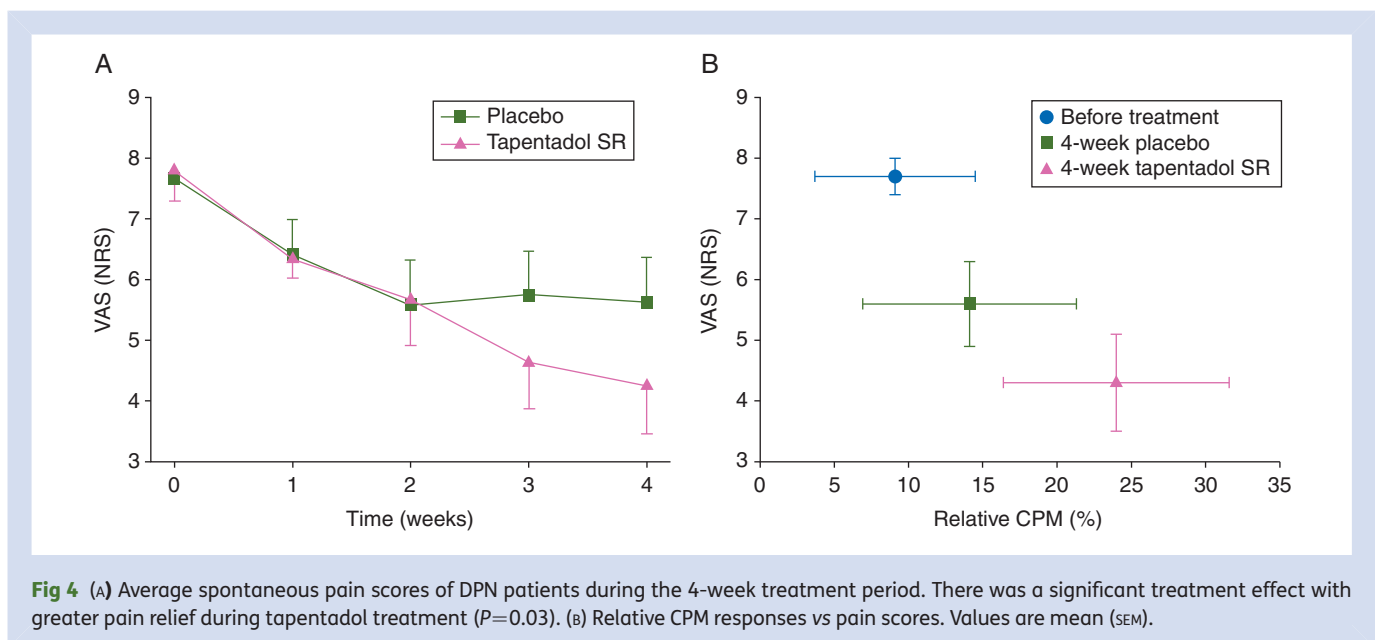
Fig 4 (A) Average spontaneous pain scores of DPN patients during the 4-week treatment period. There was a significant treatment effect with greater pain relief during tapentadol treatment ($P=0.03$). (B) Relative CPM responses *vs* pain scores. Values are mean (SEM).

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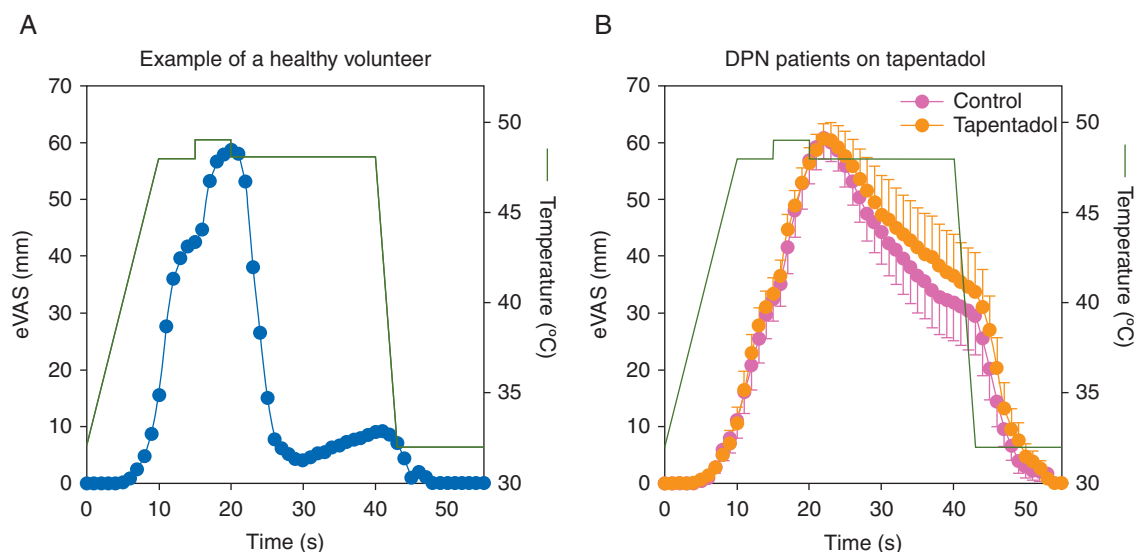
Fig 5 OA responses. (A) An example of a healthy volunteer (female, 60 yr). Data taken from Niesters and colleagues.[19] (B) Absence of tapentadol treatment on OA in painful diabetic neuropathy patients.

inhibition (NRI).[8–9 21] Through this combined mechanism of action, it is thought that tapentadol engages and potentiates descending pain inhibitory pathways,[11] although there are no human studies to substantiate this. We studied tapentadol's effect on two experimental paradigms of endogenous pain modulation (CPM and OA) in chronic pain patients with DPN. The main findings of our studies are that in DPN patients, tapentadol SR caused significant pain relief that coincided with enhanced CPM responses. No effect of tapentadol was observed on OA responses. Taking these results, we reason that relief of chronic pain in DPN patients by tapentadol is associated with engagement and potentiation of descending inhibitory pain pathways.

Conditioned pain modulation

Modulation of pain in humans involves activation of higher cortical centres (prefrontal cortex, anterior cingulate cortex, insula), brainstem (periaquaductal gray, rostral ventromedial medulla), and descending pathways projecting to the dorsal horn of the spinal cord.[1 22 27] These descending pathways may be inhibitory or excitatory. Consequently, nociceptive input that enters the spinal dorsal horn will undergo some form of modulation, either facilitation or inhibition, which results in an amplified or inhibited pain sensation at central sites. Various chronic pain syndromes show loss of descending pain inhibition, including fibromyalgia, irritable bowel syndrome, chronic tension headache, temperomandibular disorder, complex regional pain syndrome, and chronic pancreatitis.[2–5] Of importance is the finding by De Felice and colleagues[28] who showed in rodents that a genetic predisposition to activate descending inhibition protects against the development of chronic pain after peripheral nerve damage. In humans, examples of efficacious engagement of descending

inhibitory pain modulation include placebo analgesia, stress-induced analgesia, and CPM.[15–17 29 30] CPM is an experimental and consequently surrogate tool used to quantify descending pain inhibition in humans. Central inhibition of a focal noxious stimulus is induced by the administration of a noxious stimulus at a remote area (CS), thereby reducing the perception of the focal or test pain stimulus ('pain inhibits pain').[12 15] The central nature of CPM has been ascertained by the observation that specific brain regions involved in descending inhibition are activated during CPM tests in volunteers.[31 32]

Volunteer studies show that CPM engagement is less effective in women relative to men and that CPM efficacy is reduced in elderly people (starting at middle-age).[33 34] Indeed, in our middle-aged DPN patient population (mean age 59 yr), CPM was not present before the intake of study medication. Whether this is related to the underlying disease or an age-effect is unknown. Irrespective, individuals that are less able to activate CPM may have a higher probability of chronic pain development after a specific insult such as peripheral nerve damage from diabetes (cf. De Felice and colleagues)[28] or surgery. Yarnitsky and colleagues[16] showed that patients with less efficient CPM responses were at risk for development of chronic post-thoracotomy pain. The method of induction of CPM has been validated previously by us in healthy volunteers and is applied by others in chronic pain patients.[14 16]

Taking its mechanisms of action, tapentadol will interact within the descending modulatory system by activation of MORs and inhibition of neuronal norepinephrine reuptake.[7 8] Both neurotransmitter systems play an important role in the activation of descending inhibitory pain pathways at supraspinal sites and in the spinal dorsal horn (at pre- and postsynaptic sites). See Ossipov and colleagues[1] for an excellent review on this topic. For example, animal studies show that activation of MORs on brainstem nociceptive 'on-cells' will release the

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inhibition of brainstem nociceptive 'off-cells' that project to the spinal dorsal horn where nociceptive signal propagation is subsequently inhibited.[1] Activation of spinal dorsal horn pre- and postsynaptic α_2-adrenergic receptors will cause potent analgesic responses by inhibiting nociceptive afferent input. Such analgesic effects are observed after the intrathecal administration of the postsynaptic α_2-adrenergic receptor agonist clonidine.[35] Although tapentadol displays weak MOP-receptor affinity in chronic pain, animal studies show that its synergistic effect at MOP- and adrenergic-receptor systems will cause potent analgesic responses.[6 9 21] Indeed, animal studies and clinical trials show that tapentadol is an effective analgesic in a variety of chronic pain syndromes (e.g. osteoarthritis pain, low back pain, neuropathic pain).[8 11 26 36 37]

We observed that the analgesic efficacy of analgesic treatment (tapentadol/placebo) was coupled to its effect on CPM (Fig. 4). A 4-week treatment with placebo caused small analgesic effects (ΔNRS=1.7 cm) coupled to a modest increase in CPM (+14.3%), while tapentadol treatment caused a larger analgesic response (ΔNRS=3.9) coupled to a large CPM response (+24.2%). This later CPM value is similar to those observed in young healthy volunteers.[13] These findings support a mechanistic role for the endogenous analgesia system in producing effective pain relief by tapentadol, possibly by its synergistic effect at MOP and α_2-adrenergic receptors (see above). Yarnitsky and colleagues[17] showed a coupling between drug efficacy and magnitude of CPM responses for duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), in DPN patients with initially less effective CPM responses. While our small patient population, with initially minor or absent CPM responses, benefited from the 4-week tapentadol SR treatment, we remain uninformed on the efficacy of tapentadol in chronic pain patients with 'normal' CPM responses (i.e. responses of similar magnitude to those observed in young and healthy volunteers). Extrapolating the duloxetine data from Yarnitsky and colleagues would suggest that tapentadol is less effective in these patients. There is now ample evidence to argue that in painful neuropathy patients with absent or reduced CPM, CPM responses may be reactivated or potentiated by analgesic treatment that targets one or more components of the endogenous pain modulatory system.[4 17]

In chronic pain patients, the effect of tapentadol SR requires several weeks to develop (Fig. 3). Similar observations have been made for other S(N)RI-type of analgesics and tricyclic antidepressants.[38] Hence, it is recommended to evaluate the start of pain therapy with these agents not earlier than after 2 weeks of treatment.[39] Taking the similarities of mechanisms of action among these analgesics, we argue that the slow accumulation of norepinephrine at its putative effector sites may be held responsible for its slow onset of action. Our findings stress the importance of the noradrenergic component in inducing tapentadol analgesia in chronic pain as was earlier observed in animal studies.[8]

Two patients in the tapentadol group used duloxetine (duration of treatment >1 yr), a serotonin and norepinephrine reuptake inhibitor, without opioidergic activity. Theoretically, the use of this drug may have enhanced the CPM responses induced by tapentadol. However, before tapentadol treatment, these patients had no detectable CPM response and the magnitude of their CPM response after the 4-week tapentadol treatment was well within the range observed in patients not on duloxetine. We argue that these two patients did not confound the results of our study.

Offset analgesia

OA is a relatively novel model of endogenous analgesia that produces temporal alterations in pain processing. The phenomenon occurs when a small decrease (1°C) in temperature during noxious stimulation evokes a disproportionately large decrease in pain perception.[18 19] We previously assessed OA responses in a large population of volunteers aged 6–88 yr and observed response values ranging from 92% to 99%. It has been suggested that OA is of central origin as functional imaging studies show that OA activation coincides with activation of brain regions involved in the central modulation of pain.[40] However, it cannot be excluded that OA is initiated by dynamic responses of primary afferents or spinal processes. For example, Darian-Smith and colleagues[41] reported that in monkeys, the discharge of heat-sensitive nerve fibres innervating the skin was nearly completely suppressed during a 10 s 1°C cooling pulse from a baseline temperature of 39°C. A similar mechanism may occur during OA activation. A peripheral origin of OA is further supported by the observation that central acting drugs such as opioids (tapentadol, morphine, remifentanil), opioid antagonists (naloxone), and N-methyl-D-aspartate receptor antagonists (ketamine) are unable to affect OA responses in volunteers and neuropathic pain patients.[14 19 42] Finally, a recent observation that while OA is present on the forearm of healthy volunteers, it is absent on the palm of the hand further suggesting that peripheral mechanisms are important in the development of OA.[43]

We reproduce our earlier observation that OA responses are absent or reduced in patients with peripheral neuropathy.[19] The ΔeVAS values observed in the DPN patients were about 40% of those previously observed by us in healthy volunteers of the same age and sex.[19] No improvement or alteration of OA responses was observed after the 4-week tapentadol treatment, which indicates that this phenomenon of endogenous analgesia is without opioidergic or noradrenergic involvement. However, it may well be that the large and small nerve fibre damage that was present in our current population prevented their ability to discern small changes in skin temperature and consequently prevented peripheral activation of OA.

In conclusion, our results show that patients with DPN that display absent CPM responses benefit from tapentadol causing pain relief coupled to (re)activation of descending inhibitory pain pathways.

Authors' contributions

M.N. was involved in the writing of the protocol, performed the experiments, performed the data analysis, and wrote the paper. P.L.P. assisted with the experiments. L.A. assisted with the writing of the paper. E.Y.S. was involved in the writing of

the protocol and assisted with the writing of the paper. A.M.D. assisted with data analysis and writing of the paper. A.D. wrote the protocol, assisted with data analysis, and the writing of the paper.

Declaration of interest

A.D. and A.M.D. received speakers fee from Grünenthal. The other authors declare no conflicts of interest.

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Safety and Effectiveness of Topiramate for the Management of Painful Diabetic Peripheral Neuropathy in an Open-Label Extension Study

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ABSTRACT

Objective: The aim of this study was to further assess the long-term safety and effectiveness of open-label topiramate therapy in subjects with moderately to severely painful diabetic peripheral neuropathy (DPN).

Methods: Adults aged 18 to 75 years received open-label topiramate (25–600 mg/d for 26 weeks) in an extension of a previously published randomized, double-blind trial comparing topiramate with placebo. Safety analyses included adverse event (AE) reports and clinical laboratory tests. Metabolic end points included body weight and glycosylated hemoglobin (HbA_{1c}). Effectiveness analyses included a 100-mm pain visual analog (PVA) scale, worst and current pain severity, and sleep disruption.

Results: Two hundred five subjects participated in this open-label extension study (118 formerly treated with topiramate and 87 who formerly received placebo). The groups did not differ in baseline demographics or disease characteristics. One hundred twenty-four (60.5%) subjects (68.6% of former topiramate recipients and 49.4% of former placebo recipients) completed the extension study; the most common reason for discontinuation was an AE (27.3% of subjects). AEs among subjects who received ≥ 1 dose of topiramate (n = 298) included upper respiratory tract infection (16.1%), anorexia (15.1%), diarrhea (12.8%), nausea (12.8%), paresthesia (10.7%), and headache (10.1%). Baseline pain scores were lower in those formerly treated with topiramate (n = 117) than in the former placebo group (n = 86) (PVA: 43.3 vs 52.5, $P = 0.014$; worst pain: 1.9 vs 2.5, $P < 0.001$; current pain: 1.6 vs 1.9, $P = 0.026$; sleep disruption: 3.6 vs 4.6, $P = 0.021$). At the final visit, PVA, current pain,

and sleep disruption scores were not significantly different between the former topiramate and former placebo groups, but worst pain differed significantly (1.4 vs 1.8; $P = 0.025$). Mean weight loss from the start of topiramate therapy was 5.2 and 5.3 kg in the former topiramate and former placebo groups, respectively ($P < 0.001$ vs baseline). Mean HbA_{1c} values before and after topiramate treatment were 7.7% and 7.4%, respectively, in the former topiramate group ($P = 0.004$ vs baseline), and 7.6% and 7.1%, respectively, in the former placebo group ($P < 0.001$ vs baseline).

Conclusion: Although 39.5% of subjects discontinued, most often due to AEs, the results of this 26-week, open-label extension study with topiramate (up to 600 mg/d) in subjects with moderately to severely painful DPN suggest that pain relief was effective and durable. (*Clin Ther.* 2005;27:1420–1431) Copyright © 2005 Excerpta Medica, Inc.

Key words: topiramate, painful diabetic neuropathy, adverse effects, pain, body weight.

INTRODUCTION

Painful diabetic peripheral neuropathy (DPN) is a common and progressive complication of diabetes mellitus.[1,2] Meta-analyses have reported that anticonvulsants such as gabapentin, lamotrigine, and sodium

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valproate may provide greater relief of painful DPN compared with placebo,[3,4] but a search of MEDLINE (all years through May 2005) for clinical trials with the terms *pain**, *diabet**, and *neuropath** did not identify any studies of anticonvulsants for the management of painful DPN lasting beyond 12 weeks. Of the 166 publications identified by the search, 2 reported that the long-term use of capsaicin (48 weeks)[5] or tramadol (6 months)[6] was associated with effective relief of painful DPN. Additional long-term studies reported that experimental therapy with an aldose reductase inhibitor for 24 to 52 weeks (epalrestat[7] or tolrestat[8]), acupuncture for 52 weeks,[9] or acetyl-L-carnitine for 52 weeks[10] relieved the pain of DPN effectively, but other long-term studies reported that 52 weeks of therapy with a neurotrophic peptide[11] or tolrestat[12] did not relieve pain.

The anticonvulsant topiramate was associated with improved pain control in an 8-week, open-label study of 11 patients with painful DPN[13] and a 3-month, double-blind pilot study of 27 patients with painful DPN.[14] In a 12-week, randomized, double-blind, placebo-controlled, multicenter trial of 323 patients with moderately to severely painful DPN, significant reductions in pain intensity, sleep disruption, and body weight were observed in the topiramate group compared with the placebo group.[15] Mean scores on a 100-mm pain visual analog (PVA) scale decreased from 68.0 to 46.2 mm in the topiramate group and from 69.1 to 54.0 mm in the placebo group ($P = 0.038$, topiramate vs placebo). Mean scores at the final visit were similar in the topiramate and placebo groups for current pain severity (1.7 vs 1.9 on a scale from 0 to 4; $P = $ NS). Worst pain severity over the past week (2.1 vs 2.5 on a scale from 0 to 4; $P = 0.003$) and sleep disruption scores (3.9 vs 4.6 on a scale from 0 to 10; $P = 0.020$) were significantly lower in the topiramate group. Body weight decreased by 2.6 kg in the topiramate group and increased by 0.2 kg in the placebo group ($P < 0.001$).

The protocol for the 12-week, multicenter trial included this 26-week, open-label extension to further assess the long-term safety and effectiveness of open-label topiramate monotherapy in subjects with moderately to severely painful DPN.

METHODS
Study Participants
Adults aged 18 to 75 years were eligible for the initial double-blind, placebo-controlled trial if they had symmetric painful DPN and stable glycemic control for ≥3 months, and pain severity in the lower extremities ≥40 mm on a 100-mm PVA scale (0 = no pain; 100 = worst possible pain) after washout of analgesic medications. Exclusion criteria included contraindications to topiramate therapy and conditions or medications (eg, antidepressants, anticonvulsants, analgesics) that might interfere with effectiveness analyses. Subjects were randomly allocated to 12 weeks of double-blind topiramate or placebo in a 2:1 fashion.

Subjects could enroll in this open-label extension if they completed the double-blind trial or if they discontinued the double-blind trial due to lack of effectiveness after ≥8 weeks of blinded treatment with topiramate or placebo. Thirty-nine investigators (see Acknowledgments) recruited subjects at sites throughout the United States. The appropriate independent ethics committee or institutional review board at each site approved the study protocol. All subjects provided written informed consent to participate, and the study was conducted in accordance with the 1989 version of the Declaration of Helsinki.[16]

Interventions
Open-label treatment with topiramate was begun at 25 mg/d and increased to a maximum of 400 mg/d, as tolerated by the subject (**Table I**). The double-blind regimen (topiramate or placebo) from the initial study was tapered simultaneously, in the same increments by which the open-label medication was increased. This approach enabled subjects to switch from double-blind topiramate or placebo to open-label treatment with topiramate without revealing the original study medication assignment to subjects or investigators.

After the initial 8-week dose-titration period, open-label topiramate was administered without concealment; the dose could be titrated up to 600 mg/d at the discretion of the investigator. Concomitant use of other medications for pain relief (including antidepressants and anticonvulsants) was prohibited. After 26 weeks of open-label treatment, or at the time of discontinuation, the topiramate dose was tapered by approximately one third every 4 days based on the recommended schedule for the use of topiramate in epilepsy, because it was unknown whether abrupt discontinuation would precipitate rebound symptoms.[17,18]

Outcomes
Follow-up study visits were scheduled to occur after 2, 4, 8, 14, 20, and 26 weeks of open-label treatment,

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Table I. Dose-titration schedule for open-label extension of double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy.[15]

Week	Downward Titration of Double-Blind Topiramate or Placebo*	Upward Titration of Open-Label Topiramate as Tolerated†
1	Double-blind dose – 25 mg	Topiramate 25 mg
2	Double-blind dose – 50 mg	Topiramate 50 mg
3	Double-blind dose – 75 mg	Topiramate 75 mg
4	Double-blind dose – 100 mg	Topiramate 100 mg
5	Double-blind dose – 150 mg	Topiramate 150 mg
6	Double-blind dose – 200 mg	Topiramate 200 mg
7	Double-blind dose – 300 mg	Topiramate 300 mg
8	Double-blind dose – 400 mg	Topiramate 400 mg

*Double-blind regimen from a previous study (from which subjects for the present study were selected) was tapered simultaneously to allow subjects to switch from double-blind topiramate or placebo to open-label treatment with topiramate without revealing original study medication assignment. Downward titration of the double-blind medication regimen (topiramate or placebo) from the original study was continued until the dose reached 0 mg/d; the double-blind dose varied by patient at the start of open-label treatment, due to variations in tolerability of the double-blind medication regimen.
†Upward titration of open-label topiramate in the present study continued until the dose reached 400 mg/d or the maximum dose that each patient could tolerate.

and after discontinuation of study treatment. Adverse event (AE) reports were collected at each visit, either spontaneously or in response to nondirected questioning. The investigator categorized each event by relationship to topiramate treatment (*not related, doubtful, possible, probable*, or *very likely*). Investigators categorized AEs as *serious* if they were fatal or life-threatening, or if they resulted in hospitalization or disability. Cognitive function and central nervous system effects were not evaluated with specific assessment tools. Other measures included vital signs at all visits (ie, pulse, blood pressure, and weight); clinical laboratory tests performed by a central laboratory at weeks 0, 4, 8, and 26 (ie, glucose, total bilirubin, alanine aminotransferase, aspartate aminotransferase, total cholesterol, albumin, blood urea nitrogen, calcium, creatinine, uric acid, alkaline phosphatase, red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, and differential); hepatic panel at weeks 0, 12, and 20; urine pregnancy test in women at weeks 0, 8, 20, and 26; and physical examination, neurologic examination, urinalysis, and glycosylated hemoglobin (HbA_{1c}) at weeks 0 and 20.

At each follow-up visit through 26 weeks, subjects completed a 100-mm PVA scale,[19] 5-point scales for worst pain severity over the past week and current

pain severity (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme),[20] and an 11-point sleep-disruption scale (0 = does not interfere, 10 = completely interferes).[20] Subjects recorded their overall assessment of topiramate on a 5-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent) at the end of study treatment.

Statistical Analysis

The safety population included subjects who received ≥1 dose of topiramate, including subjects who participated in this open-label extension after receiving either placebo or topiramate in the original double-blind study; subjects who received topiramate in the double-blind trial but did not enter this open-label extension were also included in the safety analysis. AEs during topiramate treatment were summarized by number and percentage overall, relationship to topiramate, and association with discontinuation. Body weight and HbA_{1c} were summarized by mean change from baseline in the safety population.

The effectiveness population included subjects who received ≥1 dose of open-label topiramate and completed ≥1 effectiveness assessment during open-label treatment. Descriptive statistics were generated for baseline demographic and clinical characteristics.

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Mean values for effectiveness measures were determined at each study visit. If subjects discontinued the study, their subsequent effectiveness values were assumed to be equal to the last values recorded before discontinuation (the last-observation-carried-forward method). Power calculations were not possible because it was unknown how many patients would enter this open-label extension study; a sample size of 300 patients was estimated to provide >90% power to detect a difference of 17 mm in PVA scores between treatment groups in the original double-blind study.

Statistical comparisons of the incidence of AEs were not performed. Mean values for pain scores and metabolic end points at the final visit were compared with baseline values using simple Student t tests. Mean values for pain scores were compared between treatment groups before double-blind treatment, before open-label treatment, and after open-label treatment using simple Student t tests.

RESULTS

Study Participants

Between November 2000 and September 2002, a total of 323 subjects enrolled in the initial double-blind study,[15] and 205 subjects participated in the open-label extension (118 former topiramate recipients and 87 former placebo recipients; Figure 1). One hundred twenty-four (60.5%) subjects who enrolled in the open-label extension completed the study (68.6% [n = 81] of former topiramate subjects and 49.4% [n = 43] of former placebo subjects); the most common reason for discontinuing open-label treatment before the end of the study was an AE (21.2% [n = 25] and 35.6% [n = 31], respectively). (See next subsection for details of AEs.) There were no statistically significant differences in baseline characteristics between groups (Table II).

Tolerability

The safety population included 298 subjects who received any dose of topiramate, including 211 subjects who received double-blind topiramate (regardless of whether they entered the open-label extension) and 87 subjects in the former placebo group who received open-label topiramate (Figure 1). The mean (SD) dose of topiramate in the safety population was 204.1 (116.4) mg/d overall; the mean (SD) dose during the maintenance phase of open-label treatment was 312.1 (137.3) mg/d.

Two hundred seventy-four (91.9%) subjects reported ≥1 treatment-emergent AE after the first dose of topiramate. The most commonly reported treatment-emergent AEs were upper respiratory tract infection (16.1% [n = 48]), anorexia (15.1% [n = 45]), diarrhea (12.8% [n = 38]), nausea (12.8% [n = 38]), paresthesia (10.7% [n = 32]), and headache (10.1% [n = 30]) (Table III).

Serious AEs occurred during double-blind or open-label topiramate therapy in 33 (11.1%) subjects, including 25 (11.8%) of 211 subjects originally assigned to double-blind topiramate and 8 (9.3%) of 86 subjects originally assigned to placebo. Serious AEs included 3 cases each of back pain, injury, and basal cell carcinoma; 2 cases each of prostate disorders, cellulitis, chest pain, syncope, convulsions, neoplasm, infection, vascular disorders, and retinal detachment; and 1 case each of asthenia, ataxia, pituitary neoplasm, abdominal pain, nausea, pancreatitis, complete atrioventricular block, cardiac arrest, hyperglycemia, hyponatremia, ketosis, colon carcinoma, malignant skin neoplasm, agitation, vaginal hemorrhage, bronchitis, pleural pain, urinary retention, urinary tract infection, and unspecified AE. In addition, 1 subject in the former topiramate group died of cardiac arrest after 171 days of open-label topiramate therapy (255 total days of topiramate therapy); the subject's medical history included hypertension, hypercholesterolemia, heart murmur, and angina, and the death was not considered by the investigator to be related to topiramate treatment.

Four subjects had serious AEs that the investigator considered possibly or probably related to study treatment. A subject with no history of seizure disorder experienced seizure-like activity on day 18 of double-blind therapy; topiramate was discontinued the same day and the AE resolved within 6 days. A second subject with a history of bradycardia, coronary artery disease, and hypertension experienced moderate bradycardia and marked syncope on day 42 of the double-blind study, 1 day after discontinuing topiramate, and both events resolved the following day. A subject in the former placebo group with a history of myocardial infarction experienced marked atypical chest pain on day 36 of open-label treatment; study medication was discontinued the same day, and the subject experienced 2 seizures 2 days after discontinuation and another marked seizure 3 days after discontinuation; all seizures responded to fosphenytoin treatment, but the types of seizures were not reported. Another subject in the for-

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Figure 1. Flow diagram for subjects in open-label extension of 12-week, double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy. *Nine subjects originally assigned to double-blind topiramate discontinued due to serious adverse events. †Three subjects in the former placebo group discontinued open-label topiramate due to serious adverse events.

mer placebo group with a history of hypertension experienced marked ataxia on day 27 of open-label topiramate therapy; study medication was discontinued on day 33 and the AE resolved 59 days later.

AEs that led to discontinuation for >2% of subjects included nausea (4.0%), abnormal vision (3.4%), fatigue (3.0%), and difficulty with concentration/attention (2.3%). No cases of acute-angle glaucoma were reported.

Effectiveness

The effectiveness population included 203 subjects (117 former topiramate recipients and 86 former

placebo recipients). In the double-blind study, the mean reduction in PVA scale scores was previously reported to be significantly greater in topiramate-treated subjects than in placebo recipients (P = 0.038).[15] By the final visit of the open-label extension, mean scores on the PVA scale had decreased significantly compared with scores before open-label treatment in the former topiramate group and the former placebo group (both, P < 0.001; Figure 2). There was no significant difference in PVA scores between groups at the end of the open-label extension (Table IV).

Mean scores in both groups for the secondary end points of worst pain severity in the past week, current

Table II. Baseline demographic and clinical characteristics of subjects in open-label extension of double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy (DPN).[15]

Characteristic	Former Topiramate Group (n = 117)	Former Placebo Group (n = 86)	P
Age, mean (SD), y	59.4 (9.9)	59.1 (10.0)	0.864
Sex, no. (%)			0.572
Male	59 (50.4)	47 (54.7)	
Female	58 (49.6)	39 (45.3)	
Race, no. (%)			1.00
White	102 (87.2)	76 (88.4)	
Black	13 (11.1)	9 (10.5)	
Other	2 (1.7)	1 (1.2)	
Height, mean (SD), cm	171.1 (9.8)	170.1 (11.0)	0.512
Weight, mean (SD), kg	100.5 (21.8)	96.2 (21.0)	0.160
Duration of diabetes mellitus, mean (SD), y	10.1 (7.3)	10.5 (8.5)	0.684
Duration of painful DPN, mean (SD), y	3.4 (2.5)	3.2 (3.4)	0.694
HbA_{1c}, mean (SD), %	7.8 (1.2)	7.6 (1.2)	0.215

HbA_{1c} = glycosylated hemoglobin.

pain severity, and sleep disruption also decreased significantly during open-label topiramate treatment (all, $P < 0.001$; Table IV). Although worst pain severity decreased significantly during open-label topiramate therapy in both treatment groups, it remained significantly higher in the former placebo group than in the former topiramate group at the end of treatment ($P = 0.025$; Table IV). At the final visit, 99 (49.3%) of 201 subjects had worst pain severity of mild or none, and 126 (62.7%) of 201 subjects had current pain severity of mild or none. Patients' overall assessments of topiramate treatment at the final visit were good, very good, or excellent for 143 (71.9%) of 199 subjects (80.3% [94/117] in the former topiramate group and 59.8% [49/82] in the former placebo group).

Metabolic Effects

Body weight and HbA_{1c} values at the end of open-label treatment were compared with the values from the start of double-blind treatment in the former topiramate group and from the start of open-label treatment in the former placebo group. Weight loss occurred in 223 (76.4%) of 292 subjects. Subjects who were weighed before topiramate therapy and after

26 weeks of open-label treatment experienced mean weight loss of 5.2 and 5.3 kg in the former topiramate and former placebo groups, respectively ($P < 0.001$ vs start of topiramate therapy). Mean body weight reported at each study visit is shown in Figure 3. Mean change in body mass index (BMI) was -1.5 kg/m^2 among subjects with baseline BMI >30 kg/m^2, -0.8 kg/m^2 among those with baseline BMI >27 and $\leq$30 kg/m^2, and -0.4 kg/m^2 among those with baseline BMI $\leq$27 kg/m^2. No subject was underweight (BMI <18.5 kg/m^2) before, during, or after topiramate treatment. In the former topiramate group, mean (SD) values for HbA_{1c} before and after topiramate treatment were 7.7% (1.2%) and 7.4% (1.4%), respectively ($P = 0.004$ vs baseline). In the former placebo group, mean (SD) values for HbA_{1c} before and after topiramate treatment were 7.6% (1.2%) and 7.1% (1.3%), respectively ($P < 0.001$ vs baseline).

DISCUSSION

In this study, the high dropout rates due to AEs may have been the result of aggressive dosing. Open-label topiramate was titrated up to the target dose slowly, based on evidence that slower titration improved tol-

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Table III. Treatment-emergent adverse events reported by ≥5% of all subjects during double-blind, placebo-controlled[15] or open-label topiramate treatment (N = 298).

Event	No. (%) of Subjects
Any	274 (91.9)
Upper respiratory tract infection	48 (16.1)
Anorexia	45 (15.1)
Diarrhea	38 (12.8)
Nausea	38 (12.8)
Paresthesia	32 (10.7)
Headache	30 (10.1)
Fatigue	29 (9.7)
Dizziness	29 (9.7)
Somnolence	28 (9.4)
Injury	26 (8.7)
Hypoesthesia	26 (8.7)
Abnormal vision	26 (8.7)
Arthralgia	25 (8.4)
Weight decrease	24 (8.1)
Sinusitis	23 (7.7)
Altered taste	22 (7.4)
Constipation	20 (6.7)
Urinary tract infection	19 (6.4)
Pain	18 (6.0)
Difficulty with concentration/attention	18 (6.0)
Difficulty with memory	18 (6.0)
Back pain	17 (5.7)
Hypoglycemia	17 (5.7)
Nervousness	17 (5.7)

erability without lessening efficacy in patients with epilepsy,[21] but a high target dose of 400 to 600 mg/d was used. In previous reports, lower doses of topiramate (150–300 mg/d) were effective for the management of neuropathic pain.[22–25] Conversely, higher doses were associated with a greater risk of AEs such as cognitive dysfunction and central nervous system effects,[26] both of which contributed to withdrawal from this study. Several subjects discontinued treatment due to abnormal vision, including 2 subjects with retinal detachment, but retinopathy is a common microvascular complication of diabetes mellitus, and these 2 events were considered unrelated to topiramate. No subject had angle-closure glaucoma, a serious AE that has been reported rarely with topiramate.[27]

The most commonly reported AEs included upper respiratory tract infection, anorexia, diarrhea, nausea, paresthesia, and headache. A similar safety profile was reported during topiramate therapy in the double-blind phase of the study.[15]

Anorexia and weight decrease were commonly reported, and 223 (76.4%) of 292 subjects experienced weight loss from the beginning to the end of topiramate treatment. Weight loss was most pronounced in obese subjects, and no subject became underweight due to topiramate treatment. Topiramate was previously associated with analgesic effects and weight loss in patients with painful DPN in placebo-controlled studies,[14] including the initial 12-week, randomized, double-blind phase of this study.[15] A pooled analysis of 3 other controlled trials did not observe significant weight loss differences between topiramate and placebo during 22 weeks of double-blind treatment.[28] Aspects of the design of the latter trials may have confounded their efficacy results and have been discussed in detail previously.[15] In future placebo-controlled trials of long-term topiramate therapy for painful DPN, titration to a lower target dose and prohibition of rescue analgesia may permit identification of the minimum effective dose and the optimal balance between analgesic effects, metabolic effects, and AEs.

In this open-label extension of a randomized, double-blind clinical trial, up to 9 months of treatment with the anticonvulsant topiramate was associated with durable pain relief in subjects with moderately to severely painful DPN. A worst pain severity scale was used to measure the severity of painful flares, whereas PVA and current pain severity scales were used to provide estimates of underlying pain severity.[29] All subjects had moderately or severely painful DPN at baseline, according to a 100-mm PVA scale, but at the final pain assessment, 99 (49.3%) of 201 subjects reported worst pain severity of mild or none, and 126 (62.7%) of 201 subjects had current pain severity of mild or none. Topiramate monotherapy was associated with durable relief, as measured by statistically significant improvements in all measures of pain severity during open-label topiramate treatment (all, $P < 0.001$ vs baseline). One hundred forty-three (71.9%) of 199 subjects rated the effectiveness of long-term topiramate treatment as good, very good, or excellent overall.

The open-label study design and the inclusion/exclusion criteria could limit extrapolation of these results to other populations. In addition, the study was
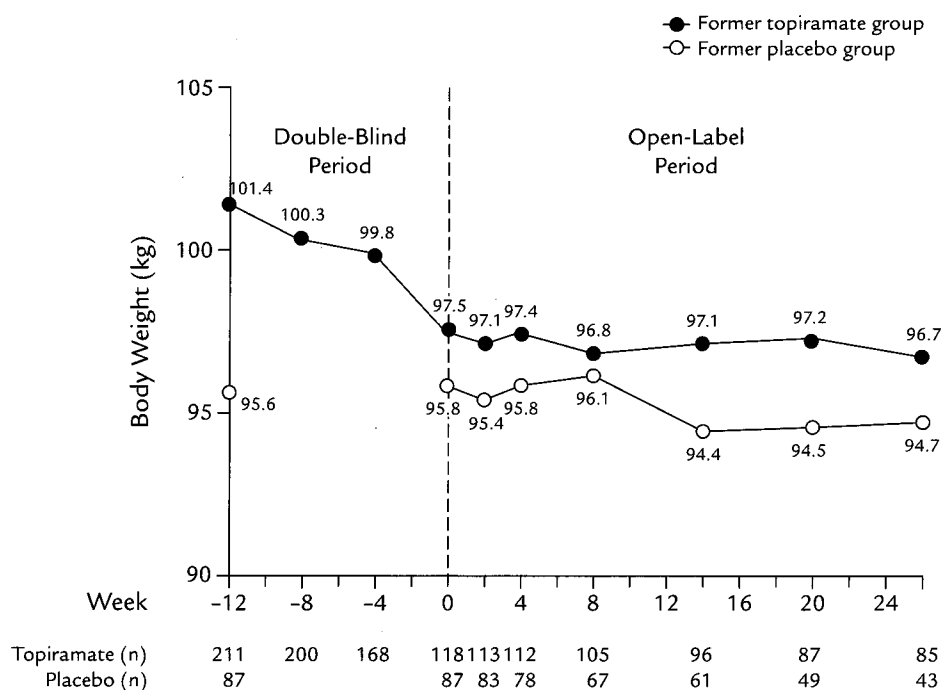
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Figure 2. Mean 100-mm pain visual analog (PVA) scores among subjects in open-label extension of 12-week, double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy. Data points represent the mean of all observed values at that visit; n values for each treatment group appear below the graph.
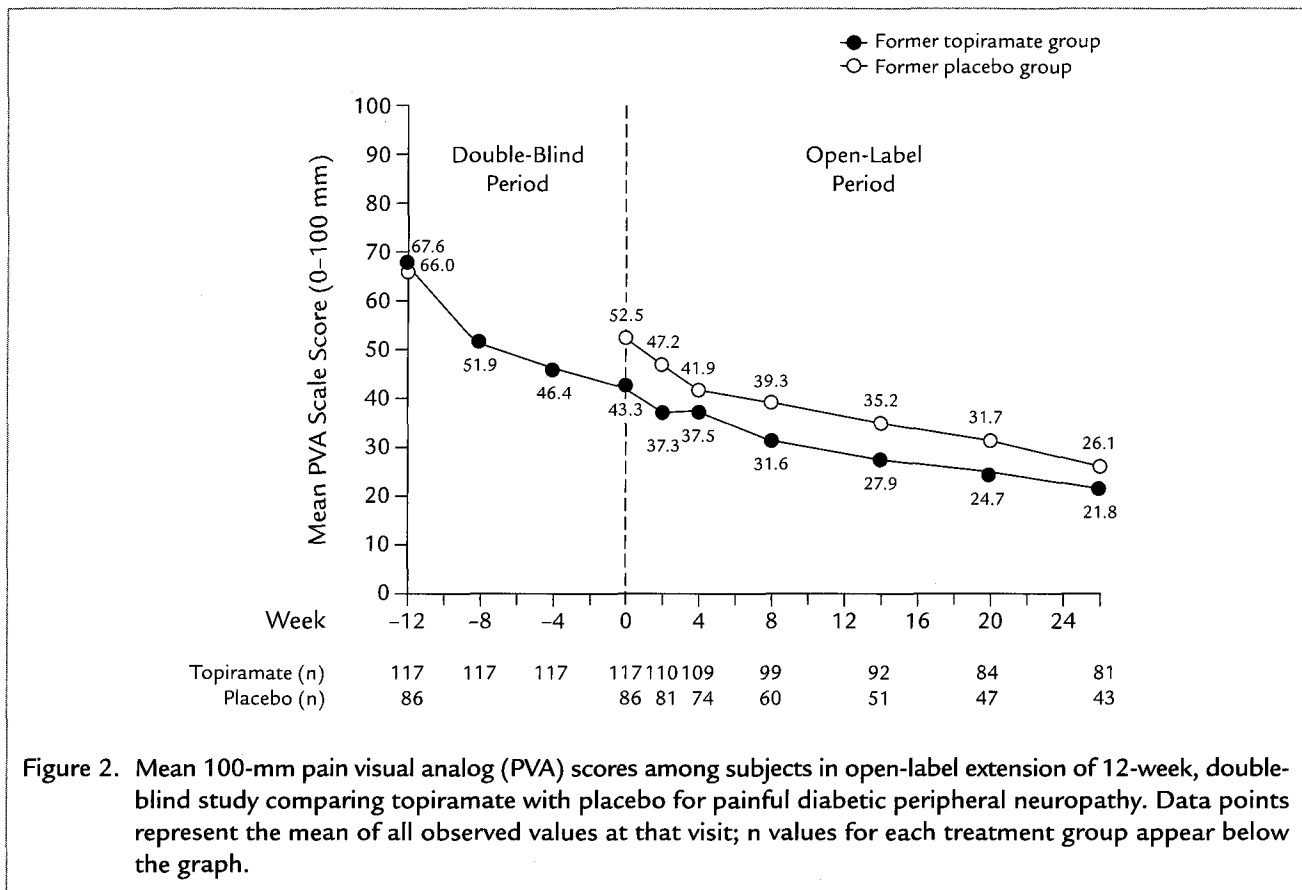
designed to assess the tolerability of therapy with topiramate, not the comparative effectiveness of switching from placebo to topiramate versus continuing topiramate therapy. Regardless of whether subjects received placebo or topiramate during the double-blind phase of the study, pain intensity and sleep interference scores improved during up to 26 weeks of open-label topiramate treatment ($P < 0.001$). Before beginning the double-blind, placebo-controlled study, pain scores and sleep interference scores were not significantly different between the treatment groups, but by the end of double-blind treatment, topiramate-treated subjects had achieved significantly lower pain intensity and sleep interference scores than placebo subjects, as reported previously.[15] By the end of this open-label extension study, subjects who switched from double-blind placebo to open-label topiramate reported final scores for pain intensity and sleep interference that were no longer significantly different from the final scores in the subjects who received topiramate throughout both phases of the study.

Subjects in the former topiramate group continued to report improvement in pain intensity and sleep disruption during the open-label extension ($P < 0.001$). One possibility is that topiramate therapy was associated with progressive pain relief. It is also possible that subjects with the least pain relief were the most likely to discontinue treatment and therefore be excluded from effectiveness evaluations at later time points. Alternately, subjects in the former topiramate group may have believed that they were switching from double-blind placebo to open-label topiramate, and thus may have anticipated even greater pain relief with open-label topiramate treatment than they had experienced with double-blind topiramate therapy.

Meta-analyses of controlled clinical trials have reported that anticonvulsants such as gabapentin, lamotrigine, and sodium valproate may be effective for the management of painful DPN.[3,4] However, no previously published trial evaluated >12 weeks of anticonvulsant treatment for painful DPN. An open-label extension of a controlled trial comparing gabapentin 600, 1200, or 2400 mg/d with placebo in 325 subjects

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Table IV. Mean (SD) pain and sleep disturbance scores among subjects in open-label extension of double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy,[15] grouped by visit and double-blind trial group.

Measure (Possible Range of Scores)	Former Topiramate Group (n = 117)	Former Placebo Group (n = 86)*	P
PVA score, mm (0–100)			
Baseline of double-blind period	67.6 (13.7)	66.0 (14.5)	0.409
Baseline of open-label period	43.3 (26.4)	52.5 (26.2)	0.014
End of open-label period	28.0 (27.0)†	35.5 (28.4)†	0.057
Worst pain severity score (0–4)			
Baseline of double-blind period	3.0 (0.7)	3.1 (0.7)	0.705
Baseline of open-label period	1.9 (1.0)	2.5 (1.0)	<0.001
End of open-label period	1.4 (1.0)†	1.8 (1.1)†	0.025
Current pain severity score (0–4)			
Baseline of double-blind period	2.2 (0.7)	2.2 (0.8)	0.961
Baseline of open-label period	1.6 (0.9)	1.9 (1.0)	0.026
End of open-label period	1.2 (1.0)†	1.4 (1.0)†	0.200
Sleep disruption score (0–10)			
Baseline of double-blind period	6.6 (2.3)	6.1 (2.4)	0.101
Baseline of open-label period	3.6 (2.9)	4.6 (2.9)	0.021
End of open-label period	2.7 (2.7)†	3.0 (2.7)†	0.393

PVA = pain visual analog.
*PVA score at end of open-label period, n = 84; worst pain severity at end of open-label period, n = 84; current pain severity at end of open-label period, n = 84; sleep disruption at end of open-label period, n = 83.
†P < 0.001 for difference versus baseline of open-label period among patients with data at both time points.

with painful DPN was not published in full, but the key findings were summarized in a review of gabapentin dosing.[30] In the 7-week, double-blind phase, gabapentin failed to achieve statistical separation from placebo; these results were consistent with the negative findings of a placebo-controlled trial of gabapentin,[31] but contradicted findings from other controlled trials in which relief was greater with gabapentin than with placebo and not significantly different from that with amitriptyline.[32,33] During the 4-month, open-label extension phase in an undisclosed number of subjects, pain intensity and sleep interference scores decreased by ~25% to ~30%.[30] Twenty-four percent of subjects had treatment-related AEs during open-label gabapentin treatment, most commonly asthenia, dizziness, and somnolence; HbA_{1c} values remained well controlled, but body weight changes were not described.[30]

A literature search identified only 2 fully published, long-term, open-label extension studies with designs similar to this study. In those studies, long-term treatment with the analgesics capsaicin[5] and tramadol[6] was associated with effective relief of painful DPN. The results of this study were similar; as in the capsaicin study,[5] approximately one half of the subjects experienced partial or complete relief of their worst pain by the final visit, and as in the tramadol study,[6] pain intensity was reduced similarly by 6 months of open-label treatment, regardless of treatment assignment in the original double-blind study. The rate of discontinuation due to treatment failure was lower in the current study (7%) and the tramadol study (3%) compared with the capsaicin study (28% over the first 24 weeks), but this was offset by a higher rate of discontinuation due to AEs in this study (27% vs 11% and 16%, respectively).

CONCLUSIONS

Although 39.5% of subjects discontinued, most often due to AEs, the results of this 26-week, open-label extension study with topiramate (up to 600 mg/d) in subjects with moderately to severely painful DPN suggest that pain relief was effective and durable.

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Figure 3. Body weight by study visit. Among subjects in open-label extension of 12-week, double-blind study comparing topiramate with placebo for painful diabetic peripheral neuropathy. Data points represent the mean of all observed values at that visit; n values for each treatment group appear below the graph.

Significant improvements in body weight and HbA_{1c} were also noted. The most frequently encountered AEs were nausea, abnormal vision, fatigue, dizziness, and difficulty with concentration/attention. The most common AEs while on treatment were upper respiratory tract infection, anorexia, diarrhea, nausea, paresthesia, and headache. Serious AEs were experienced by 11.1% of all patients.

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ORIGINAL ARTICLE

Pulsed Electromagnetic Fields to Reduce Diabetic Neuropathic Pain and Stimulate Neuronal Repair: A Randomized Controlled Trial

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ABSTRACT. Weintraub MI, Herrmann DN, Smith AG, Backonja MM, Cole SP. Pulsed electromagnetic fields to reduce diabetic neuropathic pain and stimulate neuronal repair: a randomized controlled trial. Arch Phys Med Rehabil 2009;90:1102-9.

Objective: To determine whether repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields (PEMF) targeting painful feet can reduce neuropathic pain (NP), influence sleep in symptomatic diabetic peripheral neuropathy (DPN), and influence nerve regeneration.

Design: Randomized, double-blind, placebo-controlled parallel study.

Setting: Sixteen academic and clinical sites in 13 states.

Participants: Subjects (N=225) with DPN stage II or III were randomly assigned to use identical devices generating PEMF or sham (placebo) 2 h/d to feet for 3 months.

Interventions: Nerve conduction testing was performed serially.

Main Outcome Measures: Pain reduction scores using a visual analog scale (VAS), the Neuropathy Pain Scale (NPS), and the Patient's Global Impression of Change (PGIC). A subset of subjects underwent serial 3-mm punch skin biopsies from 3 standard lower limb sites for epidermal nerve fiber density (ENFD) quantification.

Results: Subjects (N=225) were randomized with a dropout rate of 13.8%. There was a trend toward reductions in DPN symptoms on the PGIC, favoring the PEMF group (44% vs 31%; $P=.04$). There were no significant differences between PEMF and sham groups in the NP intensity on NPS or VAS. Twenty-seven subjects completed serial biopsies. Twenty-nine percent of PEMF subjects had an increase in distal leg ENFD of at least 0.5 SDs, while none did in the sham group ($P=.04$). Increases in distal thigh ENFD were significantly correlated with decreases in pain scores.

Conclusions: PEMF at this dosimetry was noneffective in reducing NP. However neurobiological effects on ENFD, PGIC and reduced itching scores suggest future studies are indicated with higher dosimetry (3000–5000 G), longer duration of exposure, and larger biopsy cohort.

Key Words: Electromagnetic fields; Rehabilitation.

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R EPETITIVE TRANSCRANIAL magnetic stimulation at the prefrontal,[1] motor,[2] and somatosensory cortex[3] is emerging as a promising alternative therapy for disabling and refractory NP. Short-term analgesic and antinociceptive effects have also been achieved with direct stimulation of the spinal cord[4] and lumbar nerve roots.[5] Both low-frequency and high-frequency magnetic stimulation can influence thermal and pain thresholds in both normative and symptomatic subjects for a short time, yet the specific mechanisms of action are yet to be determined.[6-10] Despite these preliminary data with small cohorts receiving isolated treatments only at academic clinics, there has been no information regarding its efficacy in painful DPN, which is one of the most common causes of NP. It has been estimated that 40% to 50% may experience NP.[11] DPN begins insidiously in the feet with preferential involvement of unmyelinated C fibers and small myelinated A delta fibers.[12] From a pathophysiological standpoint, DPN symptoms are believed secondary to ectopic firing of nociceptive afferent axons that are undergoing degeneration, with dysregulated expression of sodium, calcium, and potassium channels.[13-15] Skin biopsies reveal prominent cutaneous denervation with length-dependent reductions in ENFD.[16,17] The mechanisms of DPN and NP are considered multifactorial.[18] Impaired production of neurotrophic factors (NGF, IGF-I, IGF-II, fibroblast growth factor, and so forth),[19-21] impaired Schwann cells,[19,22] macrophage dysfunction,[19,23] microangiopathy with ischemia

List of Abbreviations

DPN	diabetic peripheral neuropathy
ENFD	epidermal nerve fiber density
HbA1C	glycosylated hemoglobin
IGF-I	insulin-like growth factor I
IGF-II	insulin-like growth factor II
NGF	nerve growth factor
NP	neuropathic pain
NPS	Neuropathy Pain Scale
PEMF	pulsed electromagnetic fields
PGIC	Patient's Global Impression of Change
VAS	visual analog scale
VEGF	vascular endothelial growth factor

and reduced VEGF,[19,24] impaired voltage-gated channels (sodium, potassium, calcium),[13,15,25] protein kinase C dysregulation,[19,26] and oxidative stress[19,27,28] are believed to be contributory. Data from cell culture, animal, and human studies suggest that exogenous application of weak, nonthermal electromagnetic fields upregulates NGF, IGF-I, IGF-II, fibroblast growth product, and VEGF[29-31]; reorients Schwann cells[32]; enhances macrophage activity[33] and endoneurial blood flow[34]; reduces nociceptive afferent signal transduction[35-38]; reduces free radicals[37,39] and oxidative stress[33,40]; and promotes neurite outgrowth.[35,41] Thus, magnetic stimulation may be an appropriate noninvasive intervention that could reduce DPN symptoms and produce disease modification.[35,37]

METHODS

Enrollment Criteria

The design and conduct of the randomized controlled trial is described in the accompanying consort flow diagram (fig 1). Subjects from 18 to 87 years of age with painful DPN (Dyck stage II or III)[38] with moderate-severe constant pain of 4 or higher on a 0 to 10 VAS, with a duration of at least 6 months, were recruited at 16 investigative sites in 13 states within the United States (appendix 1) between August 2005 and March 2007. Pregnant women and subjects with mechanical insulin pumps or cardiac pacemakers were excluded. Subjects could remain on their stable drug medications for diabetes and pain relief, but no new analgesics or dosing increases were permitted during the trial. Subjects were enrolled only if they were on a stable analgesic regimen. Before randomization, subjects were instructed on how to tabulate VAS (0–10) pain scores (3 times a day) and a sleep interference score (VAS 0–10, once daily). All participants provided written informed consent. Two university centers performed skin-punch biopsies at randomization and at conclusion of the study that were shipped to the University of Rochester for immunohistochemistry and measurement of ENFD.

Randomization

Demographic data (age, height, weight, sex, glycosylated hemoglobin [HbA1C], family history, duration of diabetes, concomitant medications) were collected for each enrolled subject. After entry and baseline quantification of pain and sleep interruption scores, eligible patients were randomized (1:1 via computer assignment) to receive an active coded magnetized or a sham device, identical in all characteristics except for the demagnetization procedure. Subjects agreed to use the device a maximum of 2 hours a day in divided sessions of 10 to 30 minutes for 3 months. Subjects recorded daily VAS pain and sleep scores; other outcome measures (see below) were evaluated at monthly study visits. All subjects agreed not to break the blinding of the devices. A consecutive subset of patients from 2 university sites volunteered to participate in an ENFD exploratory substudy. Three-millimeter punch skin biopsies were harvested from the proximal and distal lateral thigh, and the distal leg at baseline and after 3 months of PEMF or sham exposure. The skin biopsies were fixed, cryoprotected, sectioned, and immunostained with polyclonal antibodies to the panaxonal marker, protein gene product 9.5, according to previously published methods.[42,43] A single blind observer assessed both the linear density (fibers/mm) of nerve fibers crossing the dermal-epidermal junction ENFD (crossings) and the total linear density including intraepidermal fragments ENFD (total) from three to five 50-μM thick sections selected at random from each biopsy specimen, using previously published techniques.[44,45]
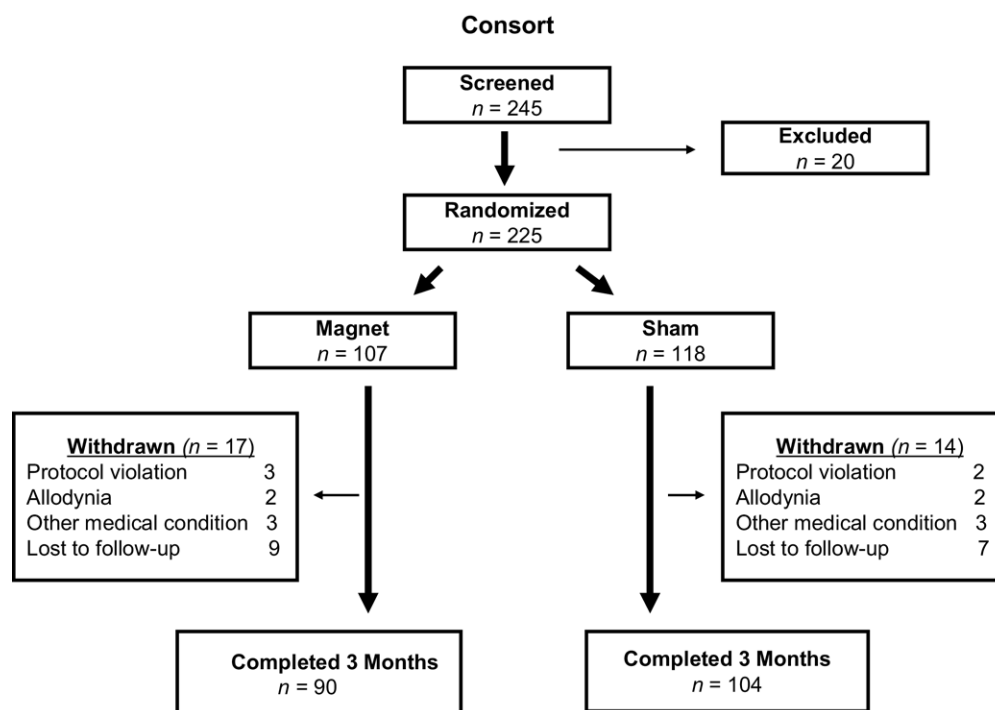
Consort

Fig 1. The CONSORT diagram revealing enrollment and outcomes. A total of 245 subjects were screened, and 225 were randomized and enrolled. A 13.8% dropout occurred (31/225) with no safety issues.
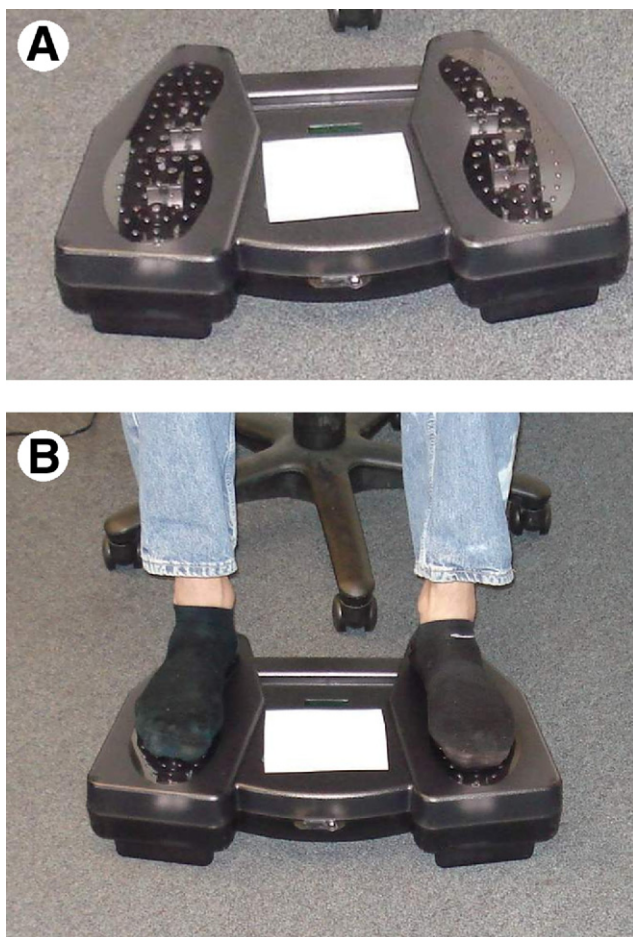
Fig 2. Device: Body Energizer.[a] (A), PEMF and/or identical sham demagnetized device. (B), Subject with feet in place.

Device

This device (fig 2) uses 6 individual (1800-G) magnetic sphere units, 3 under each foot, that are driven individually by a 6-V DC motor. A speed control circuit allows a range of 500 to 1500 revolutions per minute. The magnetic spheres turn on one axis generating magnetic lines of force (flux), and simultaneously, turn on a second axis perpendicular to the first axis (biaxial), causing the moving flux lines to cut across tissues at varying periodic angles, inducing varying intensities of force and polarity changes, resulting in static and time-varying magnetic fields. Precise placement on the foot plates with socks allows penetration of the magnetic fields up to 5 feet as measured by an ENF meter[b] (model UHS). There is exponential decay of field strength with distance from magnetic source (310,000 mG). Supersaturation of the target area from every angle at 25 times a second at maximum 1500 revolutions per minute is achieved. The barium ferrite-nylon bonded spheres do not induce any discernable sensory effects on the feet to suggest device activity.

Outcome Measures

Pain is a complex experience, and none of the existing pain scales appears to be ideal for all situations. Thus, we chose a priori to employ 3 of the most commonly used validated NP measures as outcomes for the trial.

Primary outcome. The primary outcome was a VAS (ranging from 0, no pain to 10, worst possible pain),[38] 3 times daily at the same time to represent a mean daily pain level.

Secondary outcomes. NPS assessed 10 pain descriptors collected at baseline and the end of the study.[43] NPS composite (NPS 10) scores range from 0 to 100.

PGIC[46] required subjects to select 1 of 7 options describing response to treatment, ranging from "very much improved" to "very much worse."

VAS measure of sleep disruption[38] secondary to pain was collected once on arising each morning.

Other secondary outcomes compared baseline and 12-week values of the neurologic examination (sensory, motor, reflex functions). Standardized nerve conduction velocities and amplitudes of common peroneal nerve (recording from the extensor digitorum brevis muscle) and sural nerves were monitored at baseline and the end of the study for abnormalities consistent with distal polyneuropathy. At the end of the study, both patients and investigators were asked for their perception of device activity.

Statistical Analyses

Based on prior pilot VAS pain data,[38] a sample size of 200 patients was calculated to yield a power of 80% to detect a 25% superiority of PEMF over sham placebo with alpha equal to 0.05 and beta equal to 0.20. We allowed for a dropout rate of 20% of subjects enrolled. For the NPS, 10 composite scores (range, 0–100) were used. In addition, 2 NPS items most salient to C-fiber involvement, itchy pain and burning pain (ranges, 0–10), were analyzed separately. ENFD change scores were computed by subtracting the baseline value from the 3-month value; a positive change score indicated an increase in ENFD. Change scores as continuous measures were used for correlation analyses. To assess treatment effects on ENFD, 3 categories were constructed based on a 0.5 SD of the baseline value: (1) >0.5 SD change (indicating increase in ENFD), (2) −0.5 to 0.5 (no or little change) and (3) > −0.5 SD change (decrease). The 0.5 SD criterion was chosen to be sensitive to the different levels of variability of the ENFD measures. Associations between treatment and ENFD groups were assessed with chi-square tests.

Two (PEMF, sham) $\times$ 2 (baseline to month 3) repeated-measures analyses of variance were used to assess change in pain scores and ENFD values over the course of the study. A statistically significant treatment group $\times$ time interaction indicated greater change from baseline to the end of month 3 for 1 of the treatment groups. Independent sample t tests were used to test for possible baseline differences in mean scores and for the PGIC at 3 months.

For the a priori statistical tests of the primary outcome measure, the level of significance was set at $P < .05$. For the 3 secondary outcome measures, a Bonferroni correction adjusted the statistical significance level to .017. For the Pearson product moment correlation analyses between ENFD values and pain measures, the researchers controlled for familywise error rate using a sequential Bonferroni approach: significance was set at $P < .008$. All tests were 2-sided. All analyses were conducted in an intent-to-treat manner (expectation maximization method). The Statistical Package for the Social Sciences (version 15.0[c]) was used to analyze the data.

RESULTS

The flow of patients through the clinical trial is depicted in figure 1 (CONSORT diagram). Of the 245 subjects enrolled in this study, 20 cases were initially excluded because of a low

Table 1: Baseline Demographics and Clinical Characteristics of the Enrolled Patients

Characteristic	PEMF Group (n=90)	Sham Group (n=104)
Age (y)		
Mean	61.1±10.4	60.6±12.4
Range	33–87	21–83
Weight (lb)	217.9±55.6	215.1±54.6
Height (in)	66.6±4.54	67.4±4.42
Female (%)	56.7	55.8
Years since onset of diabetes	3.9±3.0	4.0±3.0
HbA1c	7.5±1.8	7.4±1.8
Subjects with abnormal nerve conduction (%)	87.7	89.9

NOTE. Values are mean ± SD unless otherwise noted.

baseline score. Of the 225 patients randomized, there was a dropout of 31 subjects (13.8%). These included 5 because of protocol violations, 6 from diabetic complications, 16 lost to follow-up, and 4 who did not complete the study because of allodynia. Three of these 4 cases had significant premorbid burning feet syndrome with pressure allodynia. Of the 107 patients allocated to the magnet group, 90 (84.1%) completed the 3-month study, whereas 104 of the 118 allocated to the sham group (88.1%) completed the study. The dropout rate and withdrawal pattern were similar for both groups. Baseline demographics (table 1) were similar for both groups. Women represented 56.7% of the PEMF group and 55.8% of the sham group. Mean ± SD ages were 63.6±8.6 years and 63.5±9.5 years for the PEMF and sham groups, respectively. HbA1c data were similar for both groups at 3 months. There were also no changes in motor or sensory conductions or the sensory/motor neurologic examination at 3 months. Seventy-four percent of

patients who completed the study took at least 1 analgesic medication for pain, and 47% took at least 2 agents. There were no group differences in number of antiepileptic drugs, narcotics, tricyclics, selective serotonin reuptake inhibitors, or nonsteroidal anti-inflammatory drug medications taken by patients.

For the biopsy cohort (CONSORT diagram) (fig 3), of the 37 subjects enrolled in the study, 10 (27.0%) were lost to follow-up (3 magnet, 7 sham). Of the remaining 27 cases, 14 had received active magnets, and 13 had received sham devices. Women represented 64.3% of the PEMF group and 38.5% of the sham group. Mean ages were 63.6 and 63.5 years for the PEMF and sham groups, respectively.

Primary and Secondary Outcomes

Results for study outcomes are presented in table 2. There were no statistically significant group differences in baseline pain measures. For PGIC at 3 months, 43.7% of PEMF and 30.6% of sham group subjects reported very much or much improvement ($P=.04$). This result was considered a nonsignificant trend. Group differences from baseline to 3 months were not significant for VAS ($P=.96$), NPS 10 ($P=.58$), sleep scores ($P=.49$), or electrodiagnostic studies. Analyses controlling for baseline HbA1c (PEMF mean,7.5; sham mean,7.4) and whether subjects were taking insulin (10% PEMF; 28% sham) also did not reveal significant group differences. However, for subjects with moderate to severe itchy pain, there was a 53.7% reduction in mean itchy pain scores for the PEMF group from baseline to 3 months, whereas there was a 33.8% reduction for the sham group ($P=.048$). Subjects who reported higher levels of itching also reported higher levels of burning at baseline ($r=.32$; $P<.001$) and at 3 months ($r=.33$; $P<.001$).

Correlations Between Pain Measures

At baseline, the correlations between NPS 10 (only the total composite score was analyzed) and VAS was significant
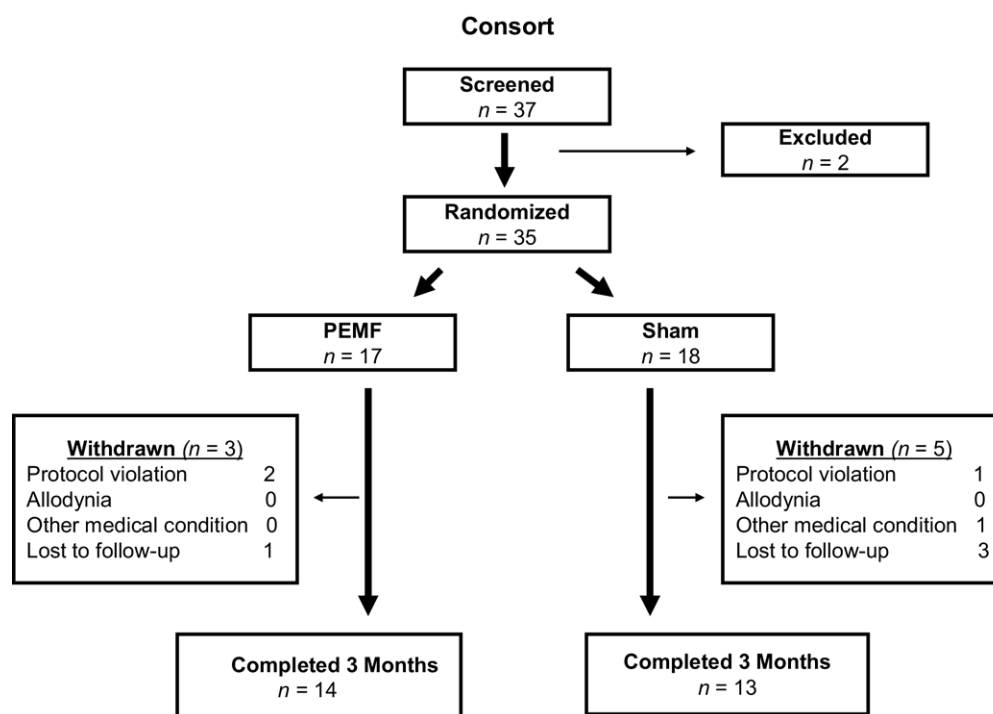
Consort

Fig 3. Biopsy consort.

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Table 2: Results of Pain and Sleep Scales

	PEMF (n=90)		Sham (n=104)	
Measures	Baseline	Month 3	Baseline	Month 3
PGIC (% much or very much improved)		43.7		30.6*
VAS	5.59±2.26	4.05±2.71	5.45±2.09	4.13±2.47
Sleep	4.63±3.14	3.27±3.08	4.23±3.14	2.96±2.85
NPS 10	60.35±17.83	45.20±21.18	56.53±18.25	44.21±20.85

NOTE. Values are mean ± SD unless otherwise noted.
*$P<.05$.

($r=.57$; $P<.001$). At 3 months, there were significant correlations between NPS 10 and VAS ($r=.77$; $P<.001$). NPS 10 and PGIC ($r=.50$; $P<.001$), and VAS and PGIC ($r=.53$; $P<.001$).

Biopsy Study

There were no statistically significant group differences in baseline ENFD measures. At the distal leg site, there was a nonsignificant trend for an increase in mean ± SD ENFD (crossings) from baseline (1.33±2.04) to 3 months (1.56±2.34) for the PEMF group, while there was a decrease in ENFD crossings from baseline (1.05±1.64) to 3 months (0.83±1.54) for the sham group ($P=.10$). Similarly, there was a nonsignificant trend for an increase in ENFD total from baseline (1.83±2.93) to 3 months (2.21±3.43) for the PEMF group, while there was a decrease in ENFD total from baseline (1.28±2.10) to 3 months (1.03±1.99) for the sham group ($P=.08$). At the distal leg site, 4 (28.6%) of the magnet group and none of the sham group had greater than 0.5 SD increase in ENFD crossings (χ^2 P value=.04; Fisher exact test=.07) (fig 4). No significant group differences were noted between baseline and 3-month values for ENFD (crossings) and ENFD (total) at the distal and proximal thigh biopsy sites. At the distal thigh, Pearson correlation coefficients for all 27 cases revealed moderate associations between 3-month PGIC scores and changes in ENFD crossings ($r=-.40$; $P=.04$) and changes in ENFD total ($r=-.41$; $P=.04$); higher nerve density was related to global improvement. Over the 3 months, an increase in distal thigh ENFD crossings was moderately associated with a decrease in NPS 10 scores ($r=-.49$; $P=.010$); an increase in distal thigh ENFD total was significantly associated with a decrease in NPS 10 scores ($r=-.53$, $P=.006$) (fig 5). There were no significant correlations between changes in distal leg or proximal thigh ENFD and VAS scores.

Blinding

At the end of the study, the perception of patients and physicians, regarding device activity was erroneous in 20% of the PEMF group and 26% of the sham group. In the absence of objective changes in neurologic examination and conduction studies, physician investigators tended to agree with the responses of their patients.

Safety

There were no safety issues or complications except that 4 cases experienced allodynia leading to dropout (sham=PEMF).

DISCUSSION

To our knowledge, this is the first multicentered, randomized, double-blind, placebo-controlled trial of cumulative exposure of PEMF targeting painful feet in subjects with NP from DPN. The results indicate that the key outcomes related to change in pain or sleep disruption were not improved by

PEMF. However, there are some provocative data suggesting that neurobiological changes occurred in the epidermal innervation exploratory substudy. First, PEMF appeared to affect
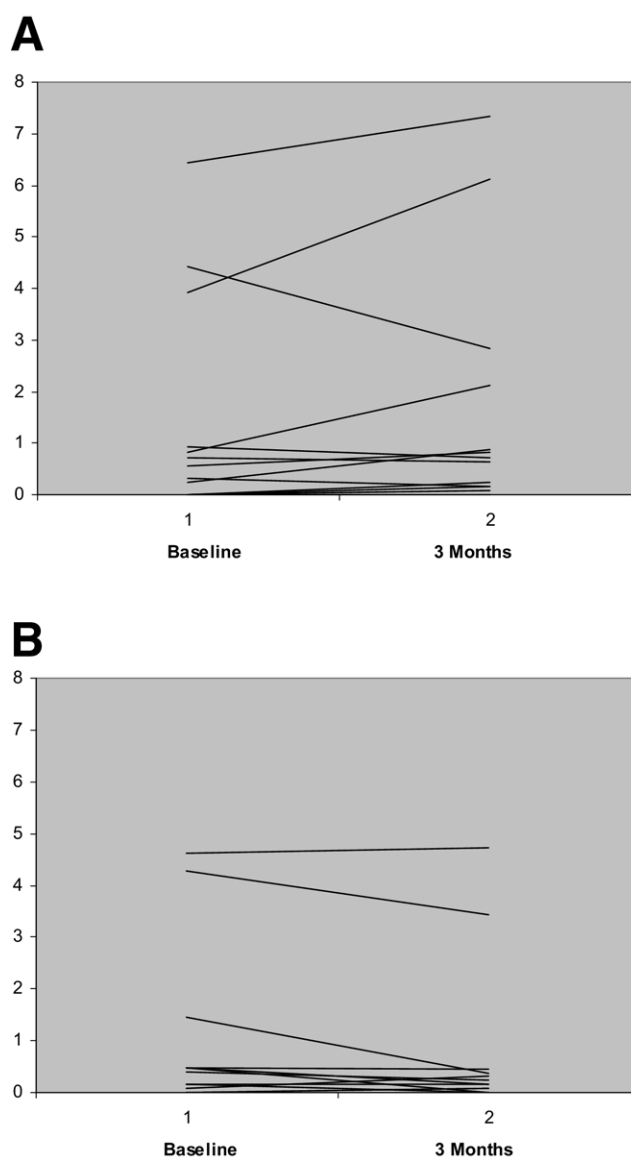
Fig 4. Number of ENFD distal leg crossings in (A) PEMF and (B) sham groups. Dark lines indicate increase in density from baseline to 3 months; light lines indicate decrease or no change.

DPN symptoms, despite the enrollment of patients with relatively advanced DPN (Dyck stage II or III), of whom many subjects were markedly deafferented, particularly at the distal leg site (table 3). Mean ± SD ENFD total for the PEMF cohort at baseline was 1.83±2.93 (normative, 16.6±5.3).[47] This suggests that cutaneous deafferentation does not preclude a beneficial effect of PEMF on NP. Second, we observed no deleterious effect of 12 weeks of PEMF on ENFD, indicating that any effects of PEMF on DPN symptoms are not mediated via injury to nociceptive afferents. Third, we found that 29% of those receiving active PEMF showed at least a 0.5 SD increase in ENFD between the pretreatment and posttreatment time points at the distal leg skin site, while none of the sham group demonstrated such an increase. The exact significance of these changes in ENFD is uncertain and should be cautiously interpreted because of the small cohort size, but it suggests the possibility of a regenerative effect. It was unfortunate that almost one third of subjects failed to return for second biopsy. The significance of reduced itchy pain scores is also unclear but was felt to represent a C-fiber function.

There are several strengths of this study. These include a large homogeneous cohort with stage II and stage III DPN. Additional strengths include the use of 3 validated pain scoring methods representing a composite of the pain experience. The high rate of study completion supports device tolerability. The inclusion of a biologic endpoint (ENFD) in a subset as another measure of neurologic safety is a strength.

Study Limitations

It is difficult to blind subjects reliably given the ease of detecting the presence of magnetism. We believe the placebo effect was as fully controlled as possible using an inert, nonactive demagnetized sham device rather than a weak magnet because biological responses have been reported. At completion of the study, the PEMF subjects (48%) reported not knowing whether they had an active or sham device; 32% believed they had an active while 20% believed they had a sham device. For the sham subjects, 56% reported not knowing

Table 3: Epidermal Nerve Fiber Density at Baseline and 3 Months

Measure	PEMF		Sham	
	Baseline	Month 3	Baseline	Month 3
Distal leg				
Crossings	1.33±2.04	1.56±2.34	1.05±1.64	0.83±1.54
Total	1.83±2.94	2.21±3.43	1.28±2.10	1.03±1.99
Distal thigh				
Crossings	5.00±1.68	4.76±2.21	4.49±1.40	4.44±2.30
Total	6.51±2.44	6.26±2.91	5.95±2.08	6.27±3.14
Proximal thigh				
Crossings	7.32±3.11	7.18±2.06	6.58±1.83	7.03±2.41
Total	9.12±3.81	10.28±3.06	8.69±2.83	9.43±3.19

NOTE. Values are mean ± SD.

whether they had an active or sham device; 26% believed they had an active device while 18% believed they had a sham device. Another limitation is that the pain reduction was reflected only in PGIC pain scales and was not significantly different in 3 of the 4 other outcome measures. This could suggest that PEMF may be influencing other aspects of neuropathic dysfunction such as paresthesiae, dysesthesiae, itching, burning, and so forth. Andre-Obadia et al[2,48] believe that pain scores after stimulation are variable and inconsistent, with their reliability increasing in the subsequent 3 to 4 days. Thus the PGIC data reflecting a cumulative response may be more meaningful than VAS and NPS.[49,50] Last, the specific structures potentially influenced in the microenvironment and specific tissue dosimetry at target areas also remain unknown.

CONCLUSIONS

This randomized controlled trial failed to demonstrate a positive effect on pain modulation at this current dosimetry and duration of exposure. However, the potential neurobiologic effects noted from PGIC and skin biopsy data (ENFD) suggest that future studies using a higher dosimetry (3000–5000 G) with a longer duration of exposure and a larger biopsy cohort is warranted to determine whether NP can be modulated by PEMF[51] and influence nerve regeneration.

APPENDIX 1: INVESTIGATORS

The site investigators are listed alphabetically with the principal investigator listed first.

- Misha M. Backonja, MD, Department of Neurology, University of Wisconsin, Madison, WI, Theresa Guiliani, RN (study coordinator)
- Frank DiPalma, DPM, Five County Foot Care, Athens, GA, Stephanie Miller (study coordinator)
- John England, MD, Billings Clinic, Billings, MT, Howard Knapp, MD, Diane Gouine, RN (study coordinator)
- Anthony Geraci, MD, Lutheran Medical Center, Queens, NY, Samara Khorchid, RN (study coordinator)
- Ghazala Hayat, MD, Department of Neurology, St. Louis University, St. Louis, MO, Susan Eller, MA, RN (study coordinator)
- David Herrmann, MD, BCH, Director of Peripheral Neuropathy Clinic and Cutaneous Innervation Laboratory, University of Rochester Medical Center, Rochester, NY, Janet Sowden, RN (study coordinator)
- Eve Holzemer, N.P. Administrative Director
- Jeffrey Jensen, DPM, Diabetic Foot and Wound Center, Denver, CO, Patricia Nelson, RN (study coordinator)
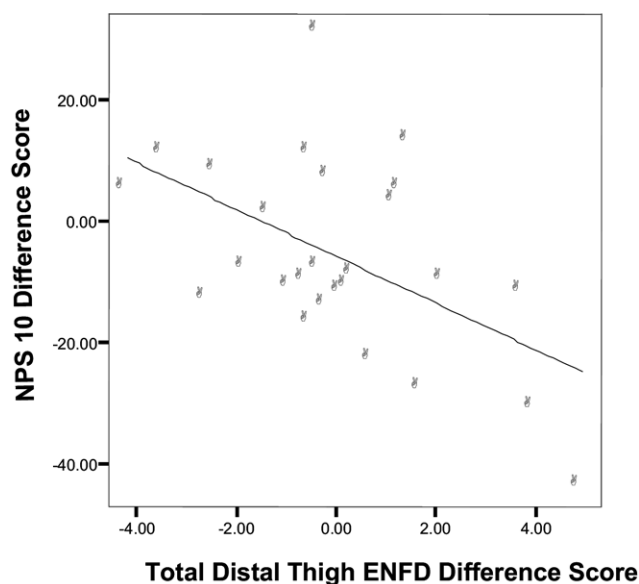

Fig 5. Scatterplot of total distal thigh ENFD: increase in ENFD was significantly associated with a decrease in NPS 10 (difference) scores ($r=-.53$; $P=.006$).

- Sam Kabbani, MD, East Tennessee Neurology Clinic, Knoxville, TN, Tara Jenkins, RN (study coordinator)
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- Keith Tyson, DPM, Jeffrey Dunkerley, DPM, Martin Foot and Ankle, Yorke, PA, Martha Martin (study coordinator)
- Michael I. Weintraub, MD, Briarcliff Manor, NY, Susan Pines Wolert (study coordinator), Christine Dee (data manager)

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Suppliers

a. Body Energizer; Nu-Magnetics, Inc, Box 572, Port Jefferson, NY 11777-1025.

b. ENF meter, Model UHS; Alpha Lab, Inc, 3005 South 300 West, Salt Lake City, UT 84115.

c. SPSS version 15.0; SPSS, Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

Static Magnetic Field Therapy for Symptomatic Diabetic Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT. Weintraub MI, Wolfe GI, Barohn RA, Cole SP, Parry GJ, Hayat G, Cohen JA, Page JC, Bromberg MB, Schwartz SL, and the Magnetic Research Group. Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehabil 2003;84:736-46.

Objective: To determine if constant wearing of multipolar, static magnetic (450G) shoe insoles can reduce neuropathic pain and quality of life (QOL) scores in symptomatic diabetic peripheral neuropathy (DPN).

Design: Randomized, placebo-control, parallel study.

Setting: Forty-eight centers in 27 states.

Participants: Three hundred seventy-five subjects with DPN stage II or III were randomly assigned to wear constantly magnetized insoles for 4 months; the placebo group wore similar, unmagnetized device.

Intervention: Nerve conduction and/or quantified sensory testing were performed serially.

Main Outcome Measures: Daily visual analog scale scores for numbness or tingling and burning and QOL issues were tabulated over 4 months. Secondary measures included nerve conduction changes, role of placebo, and safety issues. Analysis of variance (ANOVA), analysis of covariance (ANCOVA), and chi-square analysis were performed.

Results: There were statistically significant reductions during the third and fourth months in burning (mean change for magnet treatment, −12%; for sham, −3%; $P<.05$, ANCOVA), numbness and tingling (magnet, −10%; sham, +1%; $P<.05$, ANCOVA), and exercise-induced foot pain (magnet, −12%; sham, −4%; $P<.05$, ANCOVA). For a subset of patients with baseline severe pain, statistically significant reductions occurred from baseline through the fourth month in numbness and tingling (magnet, −32%; sham, −14%; $P<.01$, ANOVA)

and foot pain (magnet, −41%; sham, −21%; $P<.01$, ANOVA).

Conclusions: Static magnetic fields can penetrate up to 20mm and appear to target the ectopic firing nociceptors in the epidermis and dermis. Analgesic benefits were achieved over time.

Key Words: Diabetic neuropathies; Magnetics; Rehabilitation.

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DIABETIC PERIPHERAL NEUROPATHY (DPN) is a common and often disabling complication of diabetes mellitus (DM). Depending on criteria, DPN is estimated to occur in 50% to 90% of individuals with diabetes for more than 10 years.[1-4] As many as half of the 16 million diabetics in the United States will experience neuropathic pain at some point in their lives.[5-9] DPN begins insidiously, presenting as a symmetrical sensory polyneuropathy that follows a stocking-glove pattern. Selective involvement of unmyelinated C fibers and small myelinated A delta fibers produces pain of the burning dysesthetic type and is often accompanied by hyperalgesia and allodynia in the feet.[7,10-12] Neuropathic pain symptoms fluctuate and can be described as superficial, deep, aching, lancinating, constant, or episodic. Complaints are often worse at night. Although initial symptoms and the course of DPN vary, once neuropathic pain is established, it is almost always progressive, leading to increased discomfort and disability.[6,13-15] Furthermore, individuals with DPN are at augmented risk for foot trauma and infections that may necessitate amputative procedures.[2,16]

From a pathophysiologic standpoint, these symptoms are believed to be secondary to ectopic firing of nociceptive afferent axons that are undergoing degeneration.[7,9-12] This ectopic depolarization appears to be related to dysregulated expression of sodium and calcium channels[17-19] and a deficit in the potassium-internal rectifying channel.[20-22] Neurons at the level of the dorsal root ganglion (DRG) also become hyperexcitable after peripheral nerve injury, presumably because of loss of peripheral inhibitory influences.[23] Currently, there are no treatments that reverse or arrest progressive diabetic polyneuropathy.[24] A variety of standard oral therapies used for symptomatic neuropathic pain include tricyclic antidepressants,[25] antiepileptic medications,[26] and narcotic analgesics.[27,28] Additionally, topical products such as capsaicin[29,30] have been applied and have produced incomplete pain relief and significant side effects. Overall, the results have been disappointing and associated with significant side effects.[15,31,32] The search for reliable, safe, and effective mainstream treatments for the neuropathic pain of DPN remains a major challenge,[13,15,25-27,31-34] and, not surprisingly, patients have explored a variety of alternative approaches, including homeopathy, acupuncture, and magnetic

therapies. Spurred on by anecdotal reports, the use of permanent magnets for relief of pain has become extremely popular in recent years, with consumer spending exceeding $500 million in the United States and Canada and $5 billion worldwide.[35,36] The idea that magnetic energy from commercially available, weak magnets applied locally to the feet could influence chronic neuropathic pain may seem absurd, and yet this approach is not new.[37-41] In the absence of randomized, placebo-controlled trials, the medical community has been understandably skeptical, which has limited the acceptance of magnets as a valid option for pain relief.[42,43] However, 2 prior pilot studies successfully showed reduced neuropathic pain in 75% and 90% of patients with refractory DPN over a 4-month period, with constant application of commercial multipolar foot magnets (450G).[35,36] These surprising and unexpected favorable results prompted the present study—a nationwide, randomized placebo-controlled investigation into the legitimacy of static magnetic fields in the relief of pain from DPN.

METHODS

Enrollment Criteria

From August 1999 through January 2001, 375 subjects with symptomatic symmetrical sensory and motor diabetic peripheral neuropathy (DPN stages II or III), as defined by Dyck et al,[44,45] were recruited from 48 sites in 27 states. Consecutive patients from neurologic, podiatric, and diabetic clinics or private practice were enrolled. A few centers advertised their participation in this nationwide study to attract eligible volunteers. The primary providers were skilled clinicians who had previously participated in pharmacologic studies of diabetes and/or pain management. Enrollment criteria required that all subjects have at least 2 abnormalities on neurologic examination (sensory, motor, reflex), moderate (II) to severe (III) neuropathic pain, abnormal nerve conduction or quantitative sensory testing, and/or symptoms of autonomic dysfunction. Symptoms had to be constant and present over 6 months and refractory to various medications. Subjects included persons with insulin-dependent diabetes mellitus (IDDM) and those who were not insulin dependent (NIDDM). Subjects were excluded if other systemic diseases could potentially explain their symptoms. As a safety precaution, pregnant women and subjects who had mechanical insulin pumps or cardiac pacemakers were also excluded. Subjects tabulated validated[46-50] daily pain scores and similar, but unvalidated, quality of life (QOL) scores for 4 months and agreed that they would not attempt to break blinding of the foot devices. They also agreed to wear the devices constantly, 24 hours per day. Moderate pain was defined as scores of 5.0 to 6.99 and severe pain was defined as 7 and higher. No new analgesic drugs were allowed during the study, but individuals could remain on (or reduce) their current regimen of neuropathic pain medication. The randomized, placebo-controlled, parallel design study was fully explained to all subjects and voluntary withdrawal was allowed without prejudice.

Randomization

Demographic data (age, height, weight, gender, race, glycosylated hemoglobin [Hb A_{1c}], family history, duration of DM, complications of DM, treatment of DM) were collected at each site. Subjects completed a 2-week baseline Likert visual analog scale (VAS) quantification of their pain symptoms 3 times daily to establish a reliable mean pain score. QOL scores were recorded once daily to measure (1) sleep disturbance secondary to foot pain and (2) exercise-induced foot pain after a 10-minute exertion such as walking or other physical activity. After eligibility was confirmed and written informed consent accepted, subjects were randomized consecutively (1:1 via computer assignment) to receive an active magnetic shoe insole or a sham insole of similar appearance. Randomization was stratified by center and gender. Neither the subject nor the research staff was aware of the treatment allocation. If corrective trimming of the device was necessary to provide a comfortable fit in the shoe, a noninvolved secretary or nurse would trim them along identifiable lines around the margins. The subjects and site investigators were not present if trimming was necessary. All data were submitted to a central data bank under the supervision of the statistician who was aware of the assignments.

Magnetic Devices

The devices used in the present study are comprised of a reinforced and flexible magnetic rubber compound pressed into a sheet and cut into the shape of a shoe insole for men and women. Strontium ferrite powder is mixed into this rubber binder and magnetized with a patented pattern of alternating magnetic poles. Each pole is adjacent to and contiguous with another triangular-shaped magnetic pole of opposite polarity on each of the 3 sides of the triangle. This pattern produces a continuous array of alternating magnetic poles in every direction across the insole (fig 1).

The strength of the magnetic field is 450G, as measured with a conventional gauss meter on the surface of the insoles at the center of the triangle (10,000G=1T). The field depth of penetration is 20mm and is reduced inversely with the square of the distance. By far, the simple, most direct method of determining field strength at various distances from the insole surface is by instrument measurement. For example, using a Lakeshore 420 gauss meter with a flat transverse probe[a] has an accuracy of ±.25%. The effective field of the magnet from the insole surface is 20mm. Beyond 20mm, the magnetic field measures in the range of the ambient magnetic field of the earth at about 0.5G. The maximum surface field strength of the magnetic insole is 450G. At a 1-mm distance from the surface, the field strength drops to 249G. At 2mm, the field strength is measured at 150G. At 3mm (approximately ⅛in), the field strength is 90G. Flux density at the target area may be more clinically relevant than the magnetic reading at the surface of the magnet. The specific flux density, however, at the target area is unknown. At 13mm above the surface of the magnetized insole, the reading is only 1.5G. The sham insole's gauss meter readings did not exceed the 0.5G of the earth's magnetic field. Both sham and active magnetic shoe insoles could not be distinguished in terms of appearance, consistency, or weight. The magnetic insoles used in the present study were manufactured by Nu-Magnetics Inc,[b] and are commercially sold under the brand name of Magsteps® by Nikken Inc.[c]

Outcome Measures

Pain was measured on an 11-point numeric pain rating scale (VAS; scale range: 0, no pain; 10, worse possible pain). The primary efficacy measure was the reduction in neuropathic pain scores at week 16 compared with baseline scores. We also compared month-to-month changes. We looked specifically at 2 of the most common pain symptom scores of numbness or tingling and burning. Each symptom was recorded 3 times daily so to reduce any new variables (VAS range, 0–10). Similarly, QOL issues were considered primary efficacy measures with reduction of exercise-induced foot pain and sleep interruption secondary to pain (VAS range, 0–10). These were recorded once daily. Secondary outcomes compared baseline
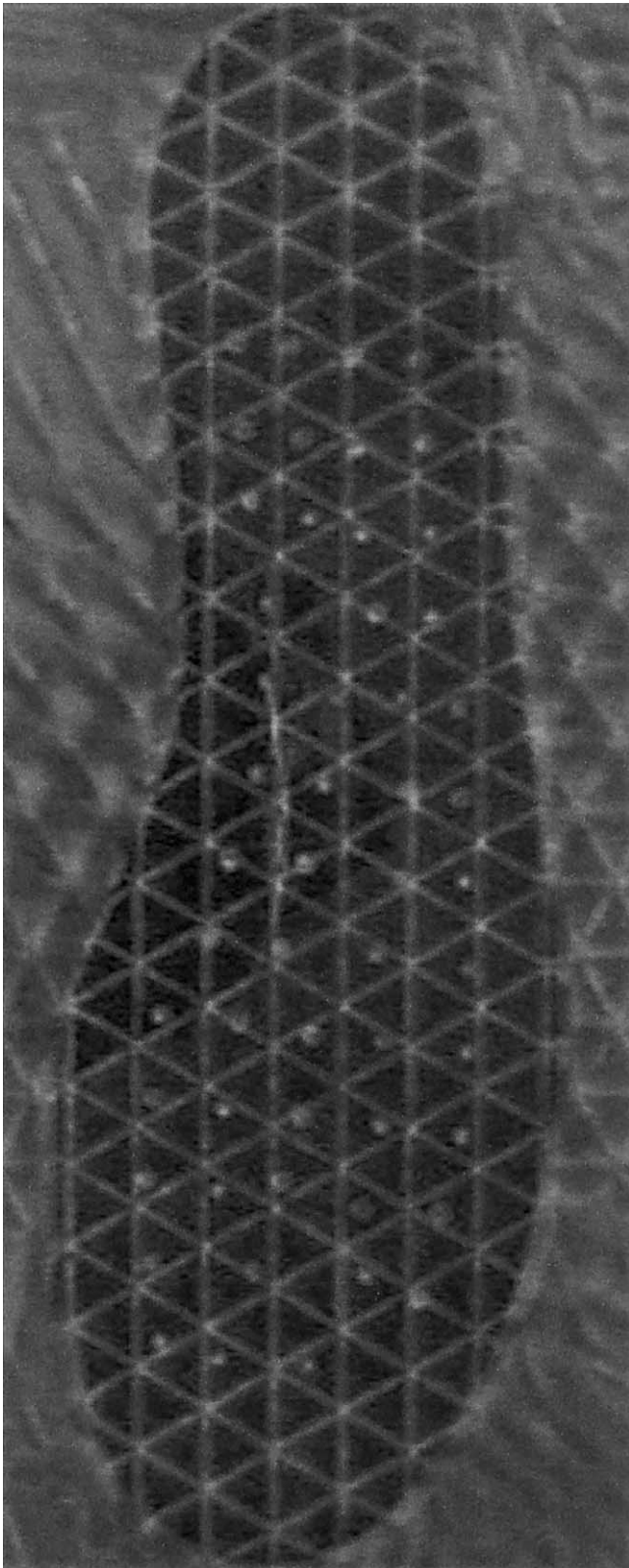
Fig 1. Magnetic field visualization with superimposed magne-view film. The microencapsulated colloidal nickel particles congregate in alignment with the magnetic flux lines producing a 2-dimensional image of the pole pattern.

and 16-week values of neurologic examinations, nerve conduction velocity (NCV), quantitative sensory testing (QST) thresholds (Neurometer[51d] or Case IV[52]), and other electrophysiologic tests.[53,54] Safety measures with tabulation of adverse events were monitored as was cause for dropouts. Additionally, an interim study performed before the end of this study at selected sites assessed masking and bias by asking patients and investigators whether they believed that a placebo or active device was used or whether they had no opinion.

Sites

There were 48 investigative sites in 27 states. They included 11 university-based centers and 37 private practices. A neurologic examination was performed before entry to identify the presence of a sensory peripheral polyneuropathy in the feet that met the Dyck[45] criteria of moderate (II) to severe (III) DPN. NCVs of the peroneal and/or posterior tibial (motor) and sural nerves (sensory) were performed in a standardized manner to confirm the presence of neuropathy. Selected sites performed forced-choice QST by using Neurometer (CPT) or Case IV equipment and other neurophysiologic tests, such as biothesiometry and sympathetic skin response (SSR). Because no standard, validated device exists and controversy about their merits surrounds the various devices, we let each site use their standard analysis technique.

Investigational Review Board

Phelps Memorial Hospital Investigational Review Board (IRB) reviewed and approved the protocol, as did IRBs at individual university centers. Phelps Memorial served as a central IRB for many investigative sites and appropriate safety and progress data were submitted to this IRB in a timely fashion. All patients provided written informed consent to participate in this study.

Statistical Analyses

For each of the 4 outcome measures (burning, numbness and tingling, foot pain, sleep scores), a 2 (treatment, sham) $\times 5$ (baseline, 1mo, 2mo, 3mo, 4mo) repeated-measures analysis of variance (ANOVA) was used to assess possible differences between treatment and sham groups over the course of the study. These analyses were followed by a 2 (treatment, sham) $\times 2$ (2mo, 4mo) analysis of covariance (ANCOVA) with baseline score as the covariate to explore treatment effects during the last 2 months of the study. Furthermore, for each outcome measure, we grouped patients into 3 categories of severity based on baseline scores. Ratings of 1 to 4 corresponded to mild pain; 5.0 to 6.99, to moderate pain; and 7 to 10, to severe pain.[55] ANOVAs were used to compare the mean changes separately for each severity group. For each of the outcome measures, chi-square tests for independence were used to assess magnet versus sham group differences in the percentage of patients who had at least a 30% reduction in severe pain. Finally, ANOVAs and ANCOVAs were used to assess treatment effects for subgroups defined by measures known to previously affect outcomes in this population. For all tests, a P value of .05 or less was considered to indicate statistical significance. Subjects with any missing data for an endpoint were excluded for that analysis.

On the basis of published results of clinical trial placebo responses for painful diabetic neuropathy,[26] at an α level of .05 and a power of .80, with 150 subjects per group, it was estimated that a difference between treatment and sham group responses of 17% or more would be statistically significant.[56] Analyses were conducted with SPSS.[e]
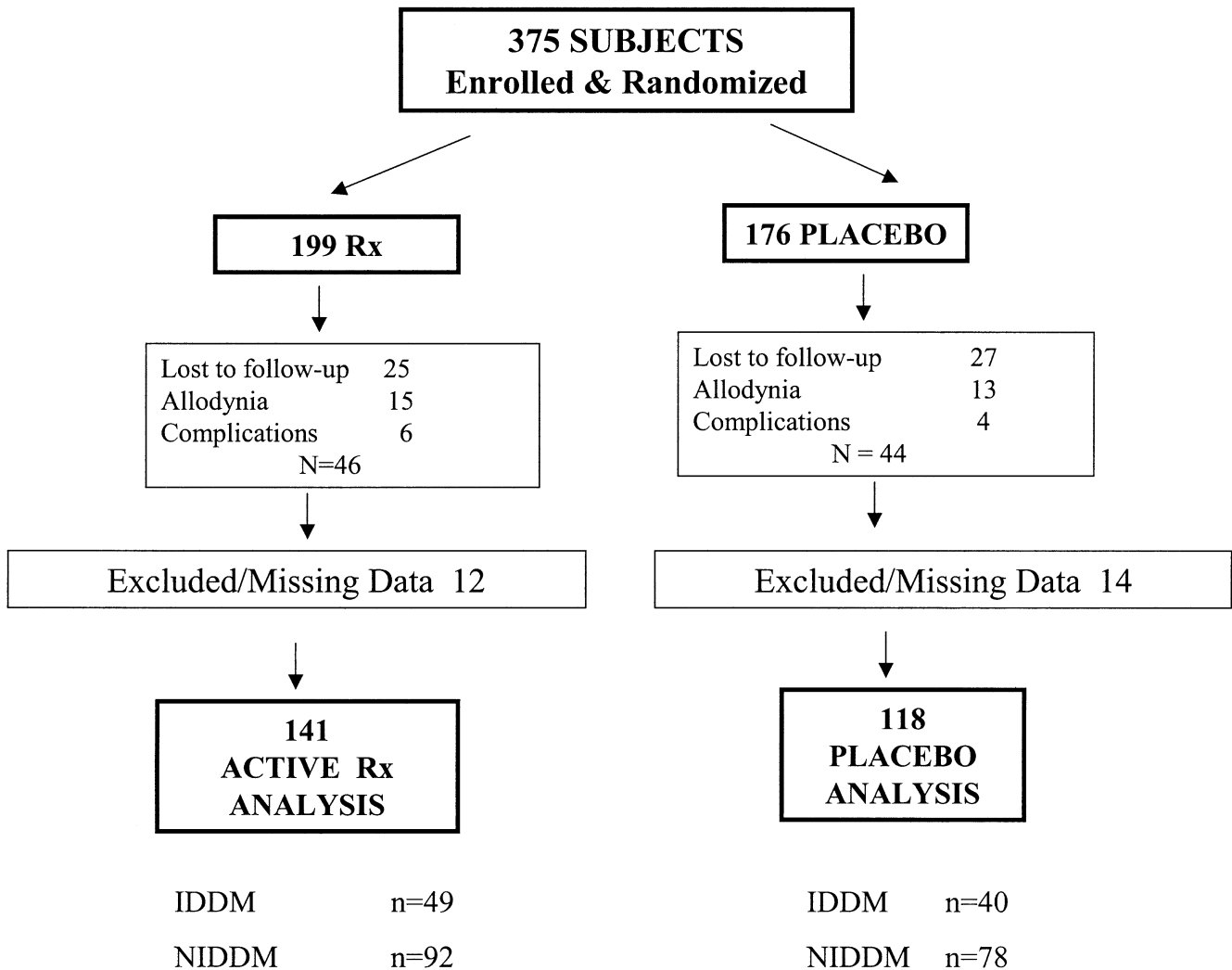
Fig 2. Flowchart of the randomized placebo-control trial. Abbreviation: Rx, treatment.

Adverse Events

Potential injury to the sole producing ulcer or abrasion or infection was monitored. Mechanical allodynia because of sensitive feet was also tabulated.

Role of Funding Source

This study was initially funded by Nu-Magnetics and supplemented by Nikken Inc. The grant recipients had complete independence regarding study design, data analysis, and manuscript preparation. The study's protocol was approved by the National Institutes of Health, but not funded.

RESULTS

The flow of patients through the clinical trial is depicted in figure 2. Three hundred seventy-five subjects were randomly assigned to treatment and sham groups, and 259 subjects (69%) successfully completed this 4-month trial. Of the 90 dropouts, 74% in the treatment group and 71% in the sham cohort dropped out before the second month. Of the total group, 45% were lost to follow-up, 24% dropped because of allodynia, and 9% dropped for nonstudy complications. Twenty-six subjects were dropped by the statistician for missing or questionable

data. The baseline characteristics for the remaining 259 subjects were similar for treatment and sham groups (table 1). The t tests for independent samples revealed no baseline differences between the treatment and sham groups for the primary end points (table 2). Racial-ethnic proportions at enrollment were a representative cross-section of the US population. In addition, a series of ANOVAs revealed no baseline differences or differences over the study period between patients at university centers and in private practice settings.

Primary Outcomes

Burning. Burning scores decreased 30% for the treatment group from baseline (mean ± standard deviation, 5.13±2.29) to month 4 (3.61±2.44) and decreased 24% for the sham group from baseline (5.27±2.40) to month 4 (4.01±2.81) (P=.000, ANOVA; fig 3). There was a larger decrease in mean scores for the treatment group (−12%) from month 2 (4.09±2.38) to month 4 (3.61±2.44) than for the sham group (−3%) from month 2 (4.12±2.65) to month 4 (4.01±2.81) (P<.05, ANCOVA).

Numbness and tingling. Numbness and tingling scores decreased 29% for the treatment group from baseline

Table 1: Baseline Characteristics of the Subjects

Characteristic	Treatment Group (n=141)	Sham Group (n=118)
Age (y)		
Mean	62.6±11.3	63.2±11.2
Range	36–85	27–85
Weight (lb)	206.7±47.0	207.1±41.2
Height (in)	67.7±4.05	67.9±4.28
Sex (n)		
Female	66	58
Male	75	60
Race (n)		
White	107	103
Nonwhite	34	15
Years since onset of diabetes	13.0±10.8	11.6±10.2
HB A_{1c}	7.7±1.8	7.6±2.1
Nerve conduction velocity (n)		
Normal	5	3
Axonal	42	31
Demy	16	14
Mixed	51	49
Insulin (n)		
Yes	49	40
No	92	78

NOTE. Values are mean ± standard deviation (SD) or as otherwise indicated.
Abbreviation: Demy, demylinating.

Fig 3. Burning mean scores for treatment and sham subjects.

(5.63±2.08) to month 4 (4.02±2.46) and decreased 22% for the sham group from baseline (5.89±2.02) to month 4 (4.57±2.58) (P=.000, ANOVA; fig 4). There was a decrease in mean scores for the treatment group (−10%) from month 2 (4.46±2.23) to month 4 (4.02±2.46) and a small increase for the sham group (+1%) from month 2 (4.54±2.58) to month 4 (4.57±2.58) (P<.05, ANCOVA). For patients with severe pain at baseline, numbness and tingling decreased 32% for the treatment group from baseline (8.17±.85) to month 4 (5.58±2.43) and decreased 14% for the sham group from baseline (8.12±.95) to month 4 (6.97±2.38) (P<.01, ANOVA; fig 5). Of the 38 treatment patients with severe pain at baseline, 27 (71%) had mild or moderate pain at month 4. In contrast, of the 40 sham patients with severe pain at baseline, 16 (40%) had mild or moderate pain at month 4 (P<.01, χ^2).

Foot pain. Foot pain scores decreased 31% for the treatment group from baseline (5.84±2.33) to month 4 (4.05±2.66) and decreased 25% for the sham group from baseline (5.76±2.29) to month 4 (4.31±2.80) (P=.000, ANOVA; fig 6). A larger decrease in mean scores existed for the treatment group (−12%) from month 2 (4.62±2.53) to month 4 (4.05±2.66) than for the sham group (−4%) from month 2 (4.47±2.68) to month 4 (4.31±2.80) (P<.05, ANCOVA). For patients with severe pain at baseline, foot pain decreased 41% for the treatment group from baseline (8.49±1.07) to month 4 (4.97±3.10) and decreased 21% for the sham group from baseline (8.35±.95) to month 4 (6.56±2.50) (P<.01, ANOVA; fig 7). Of the 40 treatment patients with severe pain at baseline, 29 (69%) had mild or moderate pain at month 4. In contrast, of the 35 sham-device patients with severe pain at baseline, 17 (49%) had mild or moderate pain at month 4. This trend in category change did not reach statistical significance (P=.07, χ^2).

Sleep. Sleep scores decreased 30% for the treatment group from baseline (4.83±2.66) to month 4 (3.36±2.76) and decreased 30% for the sham group from baseline (5.19±2.79) to month 4 (3.65±3.04) (P=.000, ANOVA; fig 8). There was a nonsignificant trend for a larger decrease in mean scores for the treatment group (−13%) from month 2 (3.83±2.83) to month

Table 2: Mean Scores for Primary Endpoints From Baseline to Month 4

Outcome Measure	n	Baseline	Month 1	Month 2	Month 3	Month 4
Burning						
Treatment	133	5.1±2.3	4.3±2.3	4.1±2.4	3.9±2.5	3.6±2.4
Sham	111	5.3±2.4	4.6±2.6	4.1±2.7	4.1±2.7	4.0±2.8
Numbness and tingling						
Treatment	137	5.6±2.1	4.7±2.2	4.5±2.2	4.3±2.4	4.0±2.5
Sham	116	5.9±2.0	4.9±2.3	4.5±2.6	4.6±2.6	4.6±2.7
Foot pain						
Treatment	121	5.8±2.3	4.9±2.4	4.6±2.5	4.2±2.6	4.1±2.7
Sham	106	5.8±2.3	4.9±2.4	4.5±2.7	4.3±2.8	4.3±2.8
Sleep						
Treatment	112	4.8±2.7	4.0±2.8	3.8±2.8	3.5±2.7	3.4±2.8
Sham	98	5.2±2.8	4.6±2.6	3.8±2.8	3.8±3.0	3.7±3.0

NOTE. Values are mean ± SD.

Fig 4. Numbness and tingling mean scores for treatment and sham subjects.

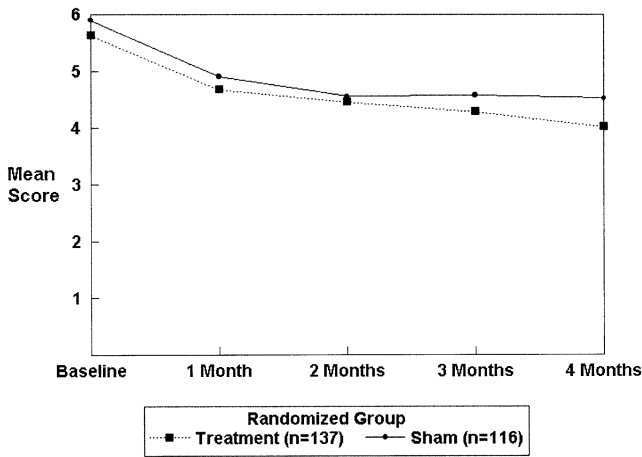**Fig 6. Foot pain mean scores for treatment and sham subjects.**

4 (3.36±2.76) than for the sham group (−3%) from month 2 (3.76±2.83) to month 4 (3.65±3.04) (*P*=.08, ANCOVA).

Secondary Outcomes

There was no evidence of deterioration of nerve function clinically or electrophysiologically in those patients reporting improvement in pain scores. Thus, there was no evidence of clinical worsening. Of the 259 subjects, 61 (24%) had Neurometer, Case IV, SSR, or biothesiometry studies. No significant differences existed between subjects in the treatment group (n=32) and those in the sham group (n=29) from baseline to 4 months on these measures.

Subgroup Analyses

For patients not taking oral antidiabetic agents, a larger decrease occurred in mean burning scores for the treatment group (−14%) from month 2 (3.81±2.38) to month 4 (3.30±2.39) than for the sham group (−1%) from month 2 (3.91±2.87) to month 4 (3.86±2.85) (*P*<.01, ANCOVA). There was a nonsignificant trend for a larger decrease in mean numbness and tingling scores for the treatment group (−10%)

from month 2 (4.26±2.21) to month 4 (3.84±2.46) than for the sham group (−1%) from month 2 (4.78±2.68) to month 4 (4.24±2.59) (*P*=.08, ANCOVA). A similar pattern was reported for patients with severe foot pain scores, with reductions of 41% and 21% for treatment and sham groups, respectively, and for numbness and tingling, with reductions of 32% and 23% for the 2 groups, respectively. Results remained significant with a Bonferroni correction.[57] By using the 30% pain reduction criterion as suggested by a Farrar stratification analysis,[58] we noted that 50% of patients with magnets had at least a 30% reduction in severe numbness and tingling, compared with 25% of patients with sham devices (*P*<.05, χ^2). Although the percentages for foot pain (32% vs 19%) and burning (42% vs 29%) were impressive, they were not statistically significant. No differences between treatment and sham groups were found based on family history of diabetes, baseline nerve conduction, or Hb A_{1c} scores.

Blinding

An interim analysis for bias and breaking the blind was performed at those active sites 6 months before study terminated (university and private practice). This analysis was to determine whether the present study was adequately blinded.

Fig 5. Numbness and tingling mean scores for subjects with baseline severe pain.
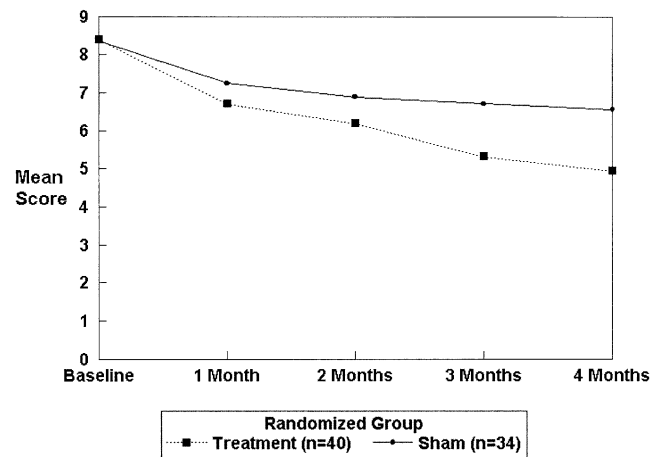
Fig 7. Foot pain mean scores for subjects with baseline severe pain.
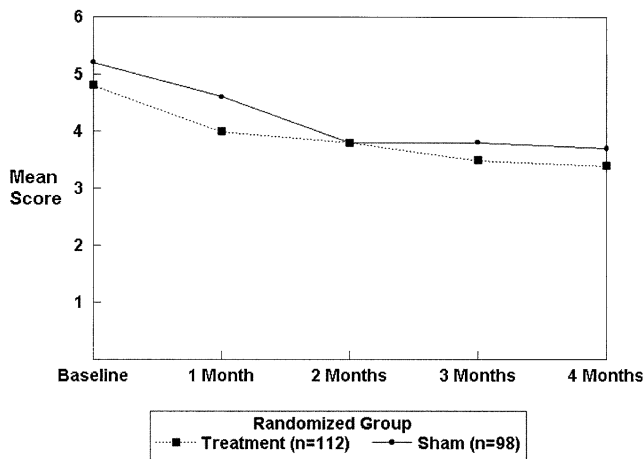
Fig 8. Sleep mean scores for treatment and sham subjects.

Subjects and examining investigators were asked at the end of the study to identify the treatment provided. Sixty-three percent of the subjects responded. Of the 83 treatment group subjects responding, 40 (48%) believed they had active magnets, 31 (37%) believed they had sham magnets, and 12 (15%) did not know. Of the 80 sham-device subjects responding, 29 (36%) believed they had active magnets, 30 (38%) believed they had sham magnets, and 21 (26%) did not know. Of 46 investigators of treatment subjects, 23 (50%) believed the subjects had active magnets, 15 (33%) believed they had sham magnets, and 8 (17%) did not know. Of 50 investigators of sham-device subjects, 22 (40%) believed the subjects had active magnets, 15 (30%) believed they had sham magnets, and 12 (26%) did not know. There was no significant association between the actual treatment received and the belief about the treatment received for subjects or investigators.

Dropouts

The dropouts were evenly represented and did not impact on the primary analysis for efficacy. We did not use the intention-to-treat (ITT) model for estimates of missing data, because 75% of the dropouts from the treatment group and 71% from the sham group dropped out before month 2. As shown in our figures, the magnetic effects became apparent after month 2; therefore, using the ITT model with most estimates based on data before month 2 would severely bias the analysis. Dropouts secondary to allodynia were equally common in both groups. Foot sensitivity is a well-known phenomenon in symptomatic patients with DPN. Thus, it is not surprising that the application of an insole (magnetized or unmagnetized) would be unpleasant to a small but significant group of patients. There were 90 dropouts (lost to follow-up, allodynia, complications) equally represented out of a sample size of 349 (25.8%). There were no mean differences between the 46 treatment and 44 sham-device patients for age, years since onset of diabetes, and baseline Hb A_{1c}, burning, numbness and tingling, foot pain, and sleep scores ($P>.05$, ANOVA). The statistician dropped 26 patients (equal representation) because of site difficulties obtaining data and unreliable data.

Safety

Measures of safety included constant reporting of adverse events and the cause for dropouts. There were no significant complications.

DISCUSSION

This is the first multicenter, double-blind, placebo-controlled study to examine the role of static magnetic fields in a homogenous cohort of DPN with neuropathic pain. The antinociceptive effect was significantly pronounced during the third and fourth month, indicating that a tonic and chronic exposure must be present to inhibit and influence sensitized afferent pain fibers. The magnitude of the reduction of burning, numbness and tingling, and exercise-induced foot pain, especially in severe and extreme cases, was comparable or superior to that observed in the gabapentin,[26] tramadol,[28] and lamotrigine[24] studies, but without side effects. Additionally, a change of 1.5 in the 0 to 10 pain scale represents a clinically meaningful difference.[59,60] This also reaffirms the data from 2 prior pilot studies.[35,36] Subset analysis identified that subjects with severe pain[55] and those not taking oral hypoglycemic agents responded more favorably than other symptomatic patients. Although our results show a statistically significant reduction in predetermined primary outcome measures, it is difficult to determine the mechanism of action responsible for these benefits. It is of interest that in the pharmacologic trials of tramadol[28] and gabapentin,[26] the subjects with severe and extreme pain responded better than other subjects. Segal et al[61] also noted in testing bipolar magnetic devices in knee pain secondary to rheumatoid arthritis that patients with mild symptoms did not respond as well. DPN pain appears to arise from an increase in afferent signals from degenerating nociceptive afferent fibers. It has been shown that early in the course of painful neuropathies, free nerve endings of nociceptive axons can disappear from the skin but are still present in the sural nerve.[62] One possibility may be that the magnetic field of these insoles somehow directly or indirectly interrupts and suppresses the afferent signal traffic of the C-fiber firing pattern of the distal part of the surviving axon thereby producing an antinociceptive effect. A number of studies have shown that DPN pain could result from depolarization because of dysregulation of normal sodium,[17-19,63] calcium,[23,64] and potassium[20] channel activities. It is well known that sodium channels accumulate in areas of axonal damage[63] and static magnetic fields have been shown to block or reduce action potential via effects on sodium flux.[65-68] A number of studies using weak pulsed, time-varying electromagnetic fields have shown biologic changes.[69-73] Adey and Chopart[74,75] considered the cell membrane as the most likely transducer modifying ion transport of protein and adenosinetriphosphatase activity. Membrane lipids with organized arrays of polar molecules, diamagnetic, have been shown to realign anisotropic molecules as well as to summate and interfere with ionic transport.[76,77] Translational movement or changes in orientation in a magnetic field can influence amplitude of evoked responses.[78,79] Because phospholipids in cell membranes have both diamagnetic and paramagnetic properties, it is clear that mechanisms exist that can produce conformational changes in various channels and structures.[80,81] However, it is not known if any of this is pertinent to putative biologic effects of static magnetic fields. Based on our data, we speculate that the kinetic activity of channeled membrane ions and blood flow in a static magnetic field is sufficiently strong to stimulate living tissues and to induce a biologic reaction. Signal transduction pathways appeared to be functionally modulated, and this is a restatement of Faraday's law of time variation.[70,82,83] It is also known that weak magnetic fields can increase the partial pressure of tissue oxygen, thereby improving oxygen delivery to tissues.[84] This property may be important because of a reported reduction in endoneurial oxygen tension in DPN.[85] Thus, it is biologically plausible

that static magnetic fields influence diabetic neurons and cell membranes of cutaneous nociceptors by amplifying the weak electromagnetic signals from the imposed and constant static magnets, thereby inducing changes in the cellular[86-88] and pericellular microenvironment.[89,90] Because these devices have a presumed penetration of up to 20mm—thereby indicating passage through the epidermal[91] and dermal layers, which contain a rich network of nerves and capillaries—we speculate that, at this site, there is inhibition and/or interruption of ectopic firing of the damaged small nociceptive afferent unmyelinated C fibers. The specific magnetic flux density at this target area is not known. Perhaps a gating response with simultaneous stimulation of the A delta fibers producing an inhibitory antinociceptive effect on C fibers occurs, compatible with Melzak–Wall hypothesis.[92] Another possibility includes the recruitment of previously passive C fibers.[93,94] Case IV studies of warm and/or cold thermal thresholds did not reveal any serial changes from baseline. Thus, at an ionic-membrane level, we can speculate that either the underlying sodium channels can be up- or down-regulated[95] or, alternatively, rapid repolarization occurs because of stimulation of the potassium internal rectifying channels.[64] This phenomenon may also produce a secondary inhibition of the firing from the DRG neurons.[23]

The major strengths of the present study include randomized, placebo design; the cooperative involvement of neurologists, podiatrists, and diabetologists; and the geographic and racial diversity of the study population. These factors suggest that the observed benefits will be applicable to the general diabetic population. Because pain levels can vary during the day, patients recorded their score 3 times daily to best derive a mean daily discomfort level and to reduce recall bias. Similarly, QOL experiences have yet to be standardized and validated by large cohorts in DPN[34]; yet, intuitively, quantification of exercise-induced foot pain and sleep disturbance represents important functional outcome measures.[96,97] Another strength is the utilization of both academic and private practice centers that not only showed good interobserver reliability, but also reduced the likelihood of selection bias.

Despite this provocative data, several limitations exist. We relied exclusively on patients' self-report for pain and outcome.[55,98] Despite favorable statistical reduction of neuropathic pain and QOL scores by wearing these devices, only modest clinical improvement was achieved. The slopes of our figures from months 2 to 4 suggest that a more potent clinical benefit could be anticipated at 8 to 12 months, and, thus, long-term studies must be performed. Another limitation was that it is a physical impossibility to blind these foot devices and to prevent the determination of magnetic activity. Subjects and investigators were advised of the importance of maintaining the blind, and the questionnaire at study termination indicates that both groups remained blinded.[99,100] Unfortunately, we were unable to identify a biologic marker using QST, SSR, and biothesiometry. None of the limitations invalidates the statistical antinociceptive effects. Intraepidermal nerve fiber density measurements were not performed and may have provided a useful pathologic correlate.[101] It has been shown that regeneration of nerve fibers can occur within 39 days in the dermis after an injury and after 4 months in the epidermis.[102,103] The observation that both refractory groups improved with lower VAS scores by 2 months compared with baseline by wearing foot devices (magnetized, unmagnetized) is provocative and similar to that seen in pharmaceutical studies and placebo trials; this suggests either a placebo response or analgesic benefit induced by foot pressure. It is possible that central regions of the brain

for pain control (ie, rostral anterior cingulate cortex, brainstem) were somehow activated.[29]

CONCLUSION

Although many questions remain about a precise mechanism of action, the present study provides convincing data confirming that the constant wearing of static, permanent, magnetic insoles produces statistically significant reduction of neuropathic pain. Considering their safety and minimal cost (<\$100), our data suggest that the insoles may be used as adjunctive or monotherapy. Future studies are needed to identify the optimal time to achieve maximum antinociceptive effect and to confirm and extend these results. Additional search for biologic markers (ie, epidermal nerve fiber biopsy, microneurography) will be necessary in future protocols to determine if permanent structural changes can be produced.

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Suppliers