SOLICITUD ANTE LA SALA ESPECIALIZADA DE PRODUCTOS FITOTERAPEUTICOS Y SUPLEMENTOS DIETARIOS SEPFSD-CR

AMPLIACIÓN DE INDICACIÓN
DE PREPARACIÓN EXISTENTE

1. RESUMEN DE LA SOLICITUD

Teniendo en cuenta la evidencia aportada, muy comedidamente nos permitimos solicitar a la Sala Especializada de Productos Fitoterapéuticos y Suplementos Dietarios SEPFSD del INVIMA, la adición de la siguiente indicación terapéutica a una preparación farmacéutica incluida en el Listado de plantas medicinales aceptadas con fines terapéuticos:

Indicación: Coadyuvante en el tratamiento del dolor neuropático

De esta manera, la información consignada para la preparación farmacéutica quedaría de la siguiente manera:

NOMBRE CIENTÍFICO
Cannabis sativa L.

NOMBRE COMÚN
Marihuana, mariguana, cáñamo, cannabis.

DROGA
Inflorescencia y brácteas

PREPARACIONES FARMACÉUTICAS
Cada pulverización en spray sublingual contiene: 2,7 mg de delta-9-tetrahidrocannabinol (THC) y 2,5 mg de cannabidiol (CBD).

Cada ml contiene: dos extractos naturales de Cannabis sativa L. folium cum flore (hoja y flor de cannabis) equivalentes a 2,7 mg de delta-9-tetrahidrocannabinol (THC) y 2,5 mg cannabidiol (CBD). (Acta 17 de 2021)

INDICACIÓN 1
Coadyuvante para la mejoría de los síntomas en pacientes con espasticidad moderada o grave debida a la esclerosis múltiple (EM) que no han respondido de forma adecuada a otros medicamentos antiespásticos y que han mostrado una mejoría clínicamente significativa de los síntomas relacionados con la espasticidad durante un período inicial de prueba del tratamiento.

INDICACIÓN 2
Coadyuvante en el tratamiento del dolor neuropático

POSOLOGÍA

Si no se observa una mejoría clínicamente significativa de los síntomas relacionados con la espasticidad durante este periodo inicial de prueba del tratamiento, deberá suspenderse el tratamiento. En los ensayos clínicos esta mejoría se definió como una mejoría de al menos el 20% en los síntomas relacionados con la espasticidad en una escala numérica de valoración (NRS) notificada por los pacientes de 0 a 10. El beneficio del tratamiento a largo plazo debe reevaluarse periódicamente.

Niños o adolescente:

No se recomienda el uso de este producto en niños o adolescentes menores de 18 años de edad debido a la ausencia de datos sobre seguridad y eficacia.

Ancianos:

No se han realizado estudios específicos en ancianos, aunque en los ensayos clínicos se han incluido pacientes de hasta 90 años de edad, sin embargo, dado que los pacientes ancianos pueden ser más propensos a desarrollar algunas reacciones adversas sobre el sistema nervioso central (SNC), debe tenerse cuidado en términos de seguridad personal, como por ejemplo durante la preparación de comidas y bebidas calientes.

Pacientes con insuficiencia hepática o renal significativa:

No se dispone de estudios en pacientes con insuficiencia hepática o renal, no obstante, en estas subpoblaciones los efectos de este producto pueden ser excesivos o prolongados. Para estas poblaciones de pacientes se recomienda efectuar una evaluación clínica frecuente.

CONTRAINDICACIONES Y ADVERTENCIAS

El producto está contraindicado en pacientes:

- Con hipersensibilidad a los cannabinoides o a alguno de los excipientes incluidos en la composición.
- Con antecedentes personales conocidos o sospechosos o antecedentes familiares de esquizofrenia u otras enfermedades psicóticas, antecedentes de trastorno grave de la personalidad u otros trastornos psiquiátricos importantes distintos de la depresión asociada a la enfermedad subyacente.
- En mujeres en periodo de lactancia, debido a la probabilidad de niveles considerables de cannabinoides en la leche materna y a los posibles efectos adversos en el desarrollo del lactante.

Advertencias

- A menudo se notifican mareos leves o moderados. Esto suele ocurrir en las primeras semanas del tratamiento.
- No se recomienda el uso de este producto en niños o adolescentes menores de 18 años de edad debido a la ausencia de datos sobre seguridad y eficacia.
- Se han observado alteraciones de la frecuencia cardiaca y en la presión arterial tras la administración de la primera dosis. Por ello, se recomienda precaución durante el periodo de ajuste de la dosis inicial. Se han observado periodos de desvanecimiento en el uso del producto. No se recomienda el uso de este producto en pacientes con enfermedad cardiovascular grave, sin embargo, tras la administración de hasta 18 pulverizaciones dos veces al día de este producto en voluntarios sanos, no se observaron cambios clínicamente relevantes en la duración de intervalos QTc, PR o QRS, la frecuencia cardiaca ni la presión arterial.

- Se debe tener cuidado al tratar pacientes con antecedentes de epilepsia o crisis recurrentes hasta que no se disponga de más información.

Se han notificado síntomas psiquiátricos como ansiedad, delusiones, cambios de humor e ideas paranoides durante el tratamiento con este producto. Es probable que estos síntomas sean el resultado de los efectos transitorios sobre el SNC, y en general, suelen ser de intensidad leve a moderada y bien tolerados. Es de esperar remitan al reducir o interrumpir el tratamiento con este producto. También se ha notificado desorientación (o confusión), alucinaciones e ideación paranoide o reacciones psicóticas transitorias, y en pocos casos, no pudo descartarse una relación causal entre la administración de este producto y la ideación suicida. En cualquiera de estas circunstancias debe interrumpirse inmediatamente el tratamiento con este producto y controlar al paciente hasta que los síntomas hayan remitido por completo.

El producto contiene aproximadamente 50% v/v de etanol. Un vaso de vino pequeño (12,5 ml) con un contenido nominal de etanol del 12% v/v contiene aproximadamente 12 g de etanol. La mayoría de los pacientes responden a dosis de hasta 12 pulverizaciones al día, que contienen menos de 0,5 g de etanol.

Existe riesgo de que aumente la incidencia de caídas en pacientes con reducción de espasticidad y cuya fuerza muscular es insuficiente para mantener la postura o la marcha. Además de un mayor riesgo a sufrir caídas, las reacciones adversas de este producto sobre el SNC, especialmente en pacientes ancianos, podrían afectar a diversos aspectos de la seguridad personal, como por ejemplo en la preparación de comidas o bebidas calientes.

A pesar de que existe un riesgo teórico en que pueda producirse un efecto aditivo con relajantes musculares como el baclofeno y las benzodiazepinas, aumentando así el riesgo de caídas, dicho efecto no se ha observado en los ensayos clínicos con este producto. No obstante, conviene advertir a los pacientes de esta posibilidad.

Mujeres en edad fértil
El producto puede reducir la eficacia de anticonceptivos hormonales.
Las mujeres en edad fértil deben utilizar un método anticonceptivo muy eficaz durante el tratamiento con este producto. Se desconoce si este producto puede reducir la eficacia de los anticonceptivos hormonales, por lo que las mujeres que los utilicen deben adoptar in método anticonceptivo adicional durante el tratamiento y durante tres meses después de su interrupción.

Es posible que los pacientes con antecedentes de abuso de sustancias psicoactivas sean más propensos a abusar también de este producto.

La interrupción brusca del tratamiento con este producto a largo plazo no da lugar a un patrón uniforme o perfil temporal de los síntomas de abstinencia o probablemente sus consecuencias se limiten a trastornos pasajeros del sueño, del estado emocional o del apetito en algunos pacientes. No se han observado incrementos en la dosificación diaria en el uso a largo plazo y los niveles de intoxicación notificados por los propios pacientes son bajos. Por ello es improbable la aparición de dependencia a este producto.

También se han observado reacciones adversas que podrían estar asociadas con la vía de administración del medicamento. Las reacciones frecuentes en el lugar de aplicación consistieron principalmente en escozor leve a moderado en el momento de la aplicación. Las reacciones frecuentes en el lugar de aplicación incluyen dolor en la zona de aplicación, dolor y molestias bucales, disgeusia, úlceras bucales y glosodinia. Se observaron dos casos de posible leucoplastia, si bien ninguno de ellos fue confirmado histológicamente, y un tercer caso no estuvo relacionado con el tratamiento. En consecuencia, se recomienda a los pacientes que experimenten molestias o úlceras en el lugar de la aplicación del medicamento, alteren de lugar en la boca y que no sigan efectuando las pulverizaciones en la zona de la mucosa dolorida o inflamada. También, se recomienda una exploración bucal periódica en el tratamiento a largo plazo. Si se observan lesiones o se notifica de dolor persistente, debe interrumpirse el tratamiento hasta la total remisión de los síntomas.

INTERACCIONES

Se ha observado in vitro que este producto es un inhibidor reversible de las enzimas CYP3A4, 1A 2, 2B6, Y 2C19 en concentraciones muy superiores a las que podrían alcanzarse clínicamente. Los estudios in vitro también demostraron que presentaba potencial para la inhibición dependiente del tiempo de la enzima CYP3A4 en concentraciones clínicamente relevantes. Se prevé que la velocidad de inactivación de la enzima CYP3A4 sea rápida.

La administración concomitante de este producto con otros sustratos de CYP3A4 puede producir un aumento de la concentración plasmática del fármaco concomitante. Se recomienda revisar la pauta posológica de dicho medicamento.

Los datos de un estudio de inducción de CYP in vitro indicaron que las concentraciones plasmáticas de THC y CBD tras las dosis clínicas de este producto podrían ser suficientes para causar la inducción de las enzimas CYP1A2, 2B6 y CYP3A4 en el ARNm. La administración concomitante de este producto con otros fármacos que se metabolizan a través de estas enzimas de citocromo P450 puede acelerar el metabolismo y reducir actividad de estos fármacos tales como los cumarínicos, las estatinas, los betabloqueantes y los corticosteroides. Se recomienda revisar la pauta posológica de los sustratos CYP sensibles cuando se administran de forma concomitante con este producto.

Enzimas UGT

En un estudio in vitro se observó que este producto inhibe enzimas UGT1A9 y UGT2B7 en concentraciones que podrían alcanzarse clínicamente. Se debe prestar atención al prescribir este producto de forma concomitante con fármacos que solo son metabolizantes por una o ambas enzimas de UGT (p, ej. propofol y determinados antivirales). Los pacientes con alteraciones genéticas de la glucuronidación (p, ej. el síndrome de Gilbert) pueden presentar una concentración sérica más elevada de bilirrubina, por lo que deben tratarse con precaución al recibir este producto de forma concomitante.

Potencial de otros fármacos para afectar a este producto

Los dos componentes principales de este producto, el delta-9-tetrahidrocanabidol (THC) y el cannabidiol (CBD), son metabolizados por el sistema enzimático del citocromo P450.

Inhibición de las enzimas del citocromo P450

El tratamiento concomitante con el inhibidor de CYP3A4 ketonazol produjo un aumento de la Cmáx. y el AUC del THC (1,2 y 1,8 veces, respectivamente), su metabolismo principal (3 y 3,6

veces, respectivamente) y el CBD (2 y 2 veces, respectivamente). Por lo tanto, si se inicia o interrumpe un tratamiento farmacológico concomitante con inhibidores de CYP3A4 (p. ej itraconazol, ritonavir, claritromicia) durante el tratamiento con este producto, podría ser necesario un nuevo ajuste de la dosis.

El tratamiento concomitante de este producto (4 pulverizaciones) con el inhibidor de CYP2C9 fluconazol (cápsula de 200 mg) produjo un aumento de la Cmáx . media y del AUC medio del THC del 22% y 32%, 6 de 15 respectivamente. La exposición al metabolito 11-OH-THC también aumentó en aproximadamente 2,1 de 2,5 veces la Cmáx. Y el AUC, respectivamente, lo que indica que el fluconazol puede inhibir su posterior metabolismo. La Cmáx del CBD también aumentó en aproximadamente el 40%, pero no hubo ningún cambio significativo en la exposición a 7-OH-CBD aunque se observó un aumento en el metabolismo circulante secundario del CBD, 6-OH CBD (de hasta 2,2 veces, según la Cmáx y el AUC). No se conoce bien la importancia clínica de esta interacción farmacológica, por lo que se debe prestar atención especial al administrar este producto de forma concomitante con inhibidores potentes de CYP2C9, dado que podría dar lugar a un aumento en la exposición al TCH, el CBD y sus metabolitos.

Inducción de las enzimas del citocromo P450
Tras el tratamiento con el inductor de CYP3A4 rifampicina, se observaron reducciones en la Cmáx. y el AUC del THC (reducción del 40% y el 20%, respectivamente), su principal metabolito (reducción del 85% y el 87%, respectivamente) y el CBD (reducción del 50% y el 60%, respectivamente). Por lo tanto, en la medida de lo posible, debe evitarse el tratamiento farmacológico concomitante con inductores enzimáticos potentes (p. ej, rifampicina, carbamazepina, fenitoína, fenobarbital, Hierba de San Juan). En caso de que se considere necesario, se recomienda un nuevo ajuste de la dosis de forma escrupulosa, sobre todo en las dos semanas posteriores a la discontinuación del tratamiento con el inductor.

General
Se debe tener cuidado al usar medicamentos hipnóticos, sedantes y fármacos con un potencial efecto sedante ya que puede producirse un efecto aditivo en la sedación y en los efectos miorrelajantes.

Aunque no se ha observado un mayor número de acontecimientos adversos en pacientes que ya tomaban fármacos antiespásticos junto con este producto, debe tenerse cuidado al administrar de forma concomitante este producto con dichos fármacos dado que puede producirse una reducción del tono y la fuerza musculares, lo que conllevaría un mayor riesgo de caídas.

El producto puede interaccionar con el alcohol y afectar a la coordinación, la concentración y la rapidez de respuesta. En general, debe evitarse el consumo de bebidas alcohólicas durante el uso de este producto, especialmente al inicio del tratamiento o al cambiar la dosis. Debe advertirse a los pacientes que los efectos aditivos sobre el SNC derivados del consumo de alcohol durante el tratamiento con este producto podrían alterar sus habilidades para conducir o utilizar máquinas y aumentar el riesgo de caídas.

Anticonceptivos hormonales
Este producto puede reducir la eficacia de los anticonceptivos hormonales sistémicos, por lo que las mujeres que utilicen este tipo de anticonceptivos deben usar un método de barrera adicional.

CÓDIGO ATC
No reportado

REFERENCIAS
INVIMA

NOTAS
Ninguna

CONDICIÓN DE VENTA DE LA PREPARACIÓN
Venta con fórmula médica

2. EVIDENCIA CIENTÍFICA

DESCRIPCIÓN DE LA PATOLOGÍA

El dolor neuropático (DN) es descrito por la Asociación Internacional para el Estudio del Dolor (IASP) como "Dolor que surge como consecuencia directa de una lesión o enfermedades que afectan al sistema somatosensorial" [1].

El dolor neuropático se produce como resultado de una reacción patológica inadaptada del sistema nervioso a un daño o lesión, y a veces se describe como dolor que se siente en ausencia de una entrada nociceptiva aferente o de estímulos nocivos que normalmente se interpretan a nivel cortical del cerebro como dolor [2].

Los tratamientos farmacológicos actuales para el dolor neuropático crónico se han limitado en gran medida a los antidepresivos tricíclicos (ATC) y los neuromoduladores (es decir, los bloqueantes de los canales de sodio y los anticonvulsivantes), pero éstos sólo han mostrado una eficacia parcial en la mayoría de los pacientes [3].

Las personas con dolor neuropático crónico luchan por encontrar opciones de tratamiento eficaces y a menudo se someten a múltiples ensayos con medicamentos de uso común en busca de un tratamiento eficaz y alivio. Existe la necesidad de explorar opciones de tratamiento adicionales para el Dolor neuropático con el creciente conocimiento y uso de los cannabinoides con fines médicos [6].

EVIDENCIA CIENTÍFICA

Luego de una extensa revisión bibliográfica se adjuntan 6 artículos relacionados con el uso de cannabinoides en el tratamiento del dolor neuropático: 2 estudios aleatorizados de grupos paralelos, doble ciego y controlados con placebo y 4 revisiones relacionadas con el manejo farmacológico del mismo. A continuación, se presenta un resumen de las referencias recopiladas:

I. **Sativex successfully treats neuropathic pain characterized by allodynia: A randomized, double-blind, placebo-controlled clinical trial.**
Turo J. Nurmikko; Mick G. Serpell; Barbara Hoggart; Peter J. Toomey; Bart J. Morlion; Derek Haines.
Published by: International Association for the Study of Pain. Elsevier B.V.
2007

Estudio multicéntrico (5 centros en el Reino Unido y 1 en Bélgica), aleatorizado, doble ciego, controlado con placebo y de grupos paralelos, de 5 semanas de duración para evaluar el efecto de Sativex® (THC: CBD) un modulador del sistema endocannabinoide sobre el dolor y la alodinia, en 125 pacientes con dolor neuropático de origen periférico, donde la mayoría eran mujeres con una edad media de 52,4 años.

Sesenta y tres pacientes fueron aleatorizados para recibir Sativex® y 62 placebo, todos ellos permanecieron con su analgesia estable preexistente. Finalizaron el estudio 88 pacientes; sólo 6 pacientes medicados con Sativex® (10%) notificaron acontecimientos adversos severos gastrointestinales (náuseas, vómitos, diarrea, estreñimiento).

Una mejoría superior al 30% en la intensidad del dolor es generalmente considerada como significativa clínicamente; este estudio demuestra que Sativex® es eficaz en el alivio del dolor neuropático periférico cuando se administra en conjunto con la medicación existente. Con Sativex®, el 26% de los pacientes experimentaron una reducción de al menos el 30% en la puntuación del dolor y el 20% de los pacientes experimentaron una reducción de al menos el 50% en la puntuación del dolor, en comparación con el 15% y el 8% de los pacientes que recibieron placebo.

Aunque los efectos terapéuticos del cannabis se han atribuido a menudo al THC, se ha demostrado que el segundo componente principal del medicamento del ensayo, el CBD, tiene efectos que pueden sumarse a los del THC en el alivio del dolor en modelos animales, y también tiene el potencial de mejorar algunos de los efectos psicoactivos del THC [4]. Esta interacción entre los dos componentes puede permitir a los sujetos tolerar dosis medias diarias de más de 27 mg de THC. Esta dosis es superior a las utilizadas en otros estudios controlados sobre el THC y puede explicar la eficacia observada [5].

II. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society.
DE Moulin, A Boulanger, AJ Clark, H Clarke, T Dao, GA Finley, A Furlan, I Gilron, A Gordon, PK Morley-Forster, BJ Sessle, P Squire, J Stinson RN, P Taenzer, A Velly, MA Ware, EL Weinberg, OD Williamson
Published by: Pain research and management
2014

En este artículo se realizó una revisión sobre los agentes analgésicos recomendados para el tratamiento del dolor neuropático crónico proporcionando una actualización basada en revisiones sistemáticas y directrices existentes sobre el tratamiento farmacológico del dolor neuropático que fueron evaluados en una reunión de consenso en mayo de 2012 y actualizados hasta septiembre de 2013.

Los medicamentos se recomendaron en la declaración de consenso si su eficacia analgésica estaba respaldada por al menos un ensayo controlado aleatorizado metodológicamente sólido (clase I o clase II) que mostrará un beneficio significativo en relación con el placebo u otro grupo de control relevante. Las recomendaciones de tratamiento se basaron en el grado de evidencia de la eficacia analgésica, la seguridad y la facilidad de uso.
Los agentes analgésicos recomendados para los tratamientos de primera línea son los gabapentinoides (gabapentina y pregabalina), los antidepresivos tricíclicos y los inhibidores de la recaptación de serotonina y noradrenalina. El tramadol y los analgésicos opioides de liberación controlada se recomiendan como tratamientos de segunda línea para el dolor moderado a intenso.

Los cannabinoides se recomiendan ahora como tratamientos de tercera línea. Los tratamientos de cuarta línea recomendados incluyen metadona, anticonvulsivantes con menor evidencia de eficacia (p. ej., lamotrigina, lacosamida), tapentadol y toxina botulínica. Los cannabinoides son agentes analgésicos con cada vez más pruebas de eficacia en estados centrales de dolor neuropático; una reciente revisión sistemática de ensayos clínicos que investigan los cannabinoides en el dolor crónico determinó que, desde 2006, ha habido siete estudios de alta calidad (clase I y II) que investigan el dolor

neuropático, la mayoría de estos estudios fueron positivos, dos ensayos incluyeron el aerosol cannabinoide para la mucosa oral SATIVEX® en el tratamiento de múltiples estados periféricos de dolor neuropático con alodinia y neuropatía diabética dolorosa. Los cannabinoides han pasado a ser agentes de tercera línea en el tratamiento de la neuralgia crónica, gracias a las pruebas cada vez más numerosas de su eficacia en múltiples modelos de dolor, como la neuropatía por VIH, la neuralgia postraumática y postquirúrgica, la neuropatía diabética dolorosa y el dolor causado por lesiones medulares.

III. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment
M. Serpell, S. Ratcliffe, J. Hovorka, M. Schofield, L. Taylor, H. Lauder, E. Ehler
Published by: European Journal of pain
2006.

El propósito de este estudio fue evaluar la eficacia de Sativex® en comparación con el placebo para aliviar el dolor neuropático periférico (DNP) asociado con alodinia. Se trató de un estudio multicéntrico, doble ciego, aleatorizado, controlado con placebo, de grupos paralelos, de 15 semanas de duración (una semana de inicio y catorce semanas de tratamiento). En total, se seleccionaron a 303 pacientes; 128 fueron asignados aleatoriamente al aerosol de THC/CBD (Sativex®) y 118 al placebo, además de su tratamiento analgésico actual. En cada visita se registró la siguiente información: acontecimientos adversos (EA), signos vitales, intoxicación 0-10 escala de valoración numérica, calidad del sueño 0-10, escala de dolor neuropático, uso de analgesia de rescate, cualquier cambio en las condiciones médicas actuales, dosis del analgésico de mantenimiento habitual, cambios en la medicación concomitante, dosis actual de la medicación del estudio y cumplimiento de la medicación.

Se tomaron muestras de laboratorio clínico (hematología, bioquímica y análisis de orina) en el cribado y al final del tratamiento. 79 pacientes con Sativex y 94 con placebo completaron el estudio y menos del 8% 10/128 presentaron algún acontecimiento adverso grave.

En conclusión, este estudio ha demostrado que, en una proporción significativa de pacientes resistentes al tratamiento, obtuvieron mejoras clínicamente importantes en el dolor, la calidad del sueño y la impresión global de cambio en la gravedad de su enfermedad mediante la administración de THC/CBD en aerosol. Además, no se observaron indicios de tolerancia y pocos pacientes declararon haber sufrido efectos adversos graves. En conjunto, estos resultados son alentadores y sugieren que el tratamiento de la PNP asociada a alodinia con THC/CBD en aerosol podría aportar beneficios significativos a los pacientes.

IV. **Pharmacologic management of chronic neuropathic pain: Review of the Canadian Pain Society consensus statement.**
Alex Mu, Erica Weinberg, Dwight E. Moulin, Hance Clarke
Published by: Pain research and management.
2017

Este artículo, se escribió para proporcionar a los médicos de familia un resumen clínico práctico de la declaración de consenso revisada de la Canadian Pain Society (CPS) sobre el tratamiento farmacológico del dolor neuropático. Un grupo de interés multidisciplinar de la CPS llevó a cabo una revisión sistemática de la literatura sobre los tratamientos actuales para el dolor neuropático para redactar la declaración de consenso revisada. Se excluyeron los estudios que: no incluían un grupo de control, tenían menos de 10 pacientes, se referían a la neuralgia del trigémino o glosofaríngea o al dolor neuropático por cáncer, excepto los síndromes de dolor posquirúrgico relacionados con el cáncer bien definidos y el dolor neuropático inducido por la quimioterapia. Se consideró que los fármacos eran de primera línea si existían pruebas de eficacia de alta calidad (al menos 1 estudio de clase I o 2 estudios de clase II consistentes -nivel de recomendación grado B o superior), si existían resultados positivos en al menos 2 modelos de dolor neuropático y si se consideraba que eran sencillos y suficientemente tolerables para su prescripción y seguimiento.

Los medicamentos de segunda o tercera línea requieren pruebas de eficacia de alta calidad, pero también requieren un seguimiento y una monitorización más especializados. Los tratamientos de cuarta línea tienen al menos un Ensayo controlado aleatorizado (ECA) con resultados positivos, pero requieren más estudios. Los gabapentinoides, los antidepresivos tricíclicos y los inhibidores de la recaptación de serotonina-norepinefrina son los fármacos de primera línea para tratar el dolor neuropático. El tramadol y otros opioides se recomiendan como agentes de segunda línea, mientras que los cannabinoides se recomiendan recientemente como agentes de tercera línea. Otros anticonvulsivantes, la metadona, el tapentadol, la lidocaína tópica y la toxina botulínica se recomiendan como agentes de cuarta línea.

Los cannabinoides han pasado de ser una opción de tratamiento de cuarta línea a una de tercera línea para el dolor neuropático crónico en las directrices de 2014 del CPS para dolor neuropático. Las formulaciones de cannabinoides en Canadá consisten actualmente en nabilona, nabiximols y cannabis seco. Las pruebas más sólidas del uso de cannabinoides son para la nefropatía por VIH, la neuropatía diabética, la nefropatía postraumática o postquirúrgica y los estados mixtos de nefropatía central y periférica.

V. **A Multicriteria Decision Analysis Comparing Pharmacotherapy for Chronic Neuropathic Pain, Including Cannabinoids and Cannabis-Based Medical Products**
David J. Nutt; Lawrence D. Phillips; Michael P. Barnes; Brigitta Brander; Helen Valerie Curran; Alan Fayaz; David P. Finn; Tina Horsted; Julie Moltke; Chloe Sakal; Haggai Sharon; Saoirse E. O'Sullivan; Tim Williams; Gregor Zorn; and Anne K. Schlag
Published by: Cannabis and cannabinoid research
2020

El tratamiento farmacológico del dolor neuropático crónico (DNC) sigue representando un importante reto clínico. El aprovechamiento colectivo tanto de la base de pruebas

científicas como de la experiencia clínica (de médicos y pacientes) puede desempeñar un papel clave a la hora de informar sobre las vías de tratamiento y contribuir al debate sobre tratamientos específicos (por ejemplo, los cannabinoides).

Este estudio se diseñó para explorar la base de pruebas sobre la utilidad clínica de los productos a base de cannabis medicinal administrados por vía oral (incluidos los extractos de cannabis y los medicamentos a base de cannabis como los nabiximols [Sativex está aprobado en 30 países, pero no se comercializa en todos] dronabinol y nabilona) para el tratamiento del Dolor Neuropático Crónico en adultos. En la conferencia de decisión, los participantes estuvieron de acuerdo en que el potencial de los medicamentos a base de cannabis administrados por vía oral para tratar el dolor crónico neuropático de más de 3 meses de duración en adultos, en lugar de la definición más amplia de "dolor crónico", era una cuestión clave, en gran medida porque hay más pruebas publicadas sobre los medicamentos a base de cannabis solos o en comparación con otros medicamentos aprobados para el dolor crónico neuropático que las que existen para otros síndromes de dolor. Los productos con una proporción 1:1 de D9-tetrahidrocannabinol (THC): cannabidiol (CBD) -p. ej., Sativex o extractos 1:1 de THC: CBD administrados por vía oral o sublingual- obtuvieron la puntuación global más alta (basada en la seguridad y los beneficios), seguidos de los de CBD dominante y, a continuación, los de THC dominante.

Cada vez se reconoce más el impacto de los CBMP en la mejora de la calidad de vida de los pacientes. Los perfiles de beneficios y seguridad de los cannabinoides fueron superiores a los de otros medicamentos de uso común para el dolor neuropático crónico, en gran medida porque contribuyen más a la calidad de vida y tienen un perfil de efectos secundarios más favorable; los resultados también reflejan las deficiencias de los tratamientos farmacológicos alternativos con respecto a la seguridad y mitigación de los síntomas del dolor neuropático, en comparación con otras sustancias utilizadas para el manejo del Dolor Neuropático Crónico por lo que deberían incluirse en el armamento de los especialistas clínicos.

VI. Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis.
Sainsbury B, Bloxham J, Pour MH, Padilla M, Enciso R.
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2021

La estrategia de búsqueda inicial a través de bases de datos inició el 5 de febrero de 2020; produjo 513 referencias y 9 referencias adicionales identificadas a través de una búsqueda manual. Una vez eliminados los duplicados, se examinaron 370 registros y se redujeron a 32 manuscritos relevantes. Los estudios incluidos en esta revisión sistemática se limitaron a publicaciones en inglés de ensayos aleatorios controlados con placebo. Se excluyeron de esta revisión los estudios identificados sin control con placebo, sólo con resúmenes, en otro idioma diferente al inglés, con afecciones distintas de dolor neuropático y en los que los medicamentos cannabinoides eran sólo coadyuvantes y los estudios duplicados.

La búsqueda en las bases de datos finalizó el 2 de enero de 2021, produjo 379 registros con 17 ensayos controlados aleatorios incluidos (861 pacientes con dolor neuropático). Según se informa, el cannabis contiene más de 450 compuestos, de los cuales 70 se clasifican como fitocannabinoides. El Delta 9-THC es el principal componente activo, con

propiedades psicoactivas (por ejemplo, reducción de la ansiedad y el estrés) y analgésicas. El cannabidiol (CBD) es otro componente de interés. Los estudios han demostrado que el CBD tiene una menor afinidad por los receptores CB y puede contrarrestar los efectos indeseables del THC sobre la memoria, la cognición y el estado de ánimo, pero también puede tener un efecto sobre la modulación del dolor gracias a sus propiedades antiinflamatorias.

El metanálisis demostró que se produjo una reducción significativa de la intensidad del dolor con THC/CBD, THC y dronabinol en comparación con placebo. Los pacientes que tomaban THC/CBD tenían 1,756 veces más probabilidades de lograr una reducción del dolor del 30% y 1,422 veces más probabilidades de lograr una reducción del 50%, que los que tomaban placebo. Los pacientes que recibieron THC tuvieron un 21% más de mejoría en la intensidad del dolor y 1,855 veces más probabilidades de lograr una reducción del dolor del 30% que con placebo.

REFERENCIAS

1. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain 2011; 152: 2204-5.

2. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers 2017; 3: 17002.

3. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999; 83: 389-400.

4. Russo EB, McPartland JM. Cannabis is more than simply Delta (9)-tetrahydrocannabinol. Psychopharmacology (Berl) 2003; 165:431–2.

5. Guy GW, Robson P. A Phase I, a double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis-based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers. J Cannab Ther 2003; 3:121–52.

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Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

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Abstract

Cannabinoids are known to have analgesic properties. We evaluated the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia, in 125 patients with neuropathic pain of peripheral origin in a five-week, randomised, double-blind, placebo-controlled, parallel design trial. Patients remained on their existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Sixty-three patients were randomised to receive sativex and 62 placebo. The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores −1.48 points vs. −0.52 points on a 0–10 Numerical Rating Scale ($p = 0.004$; 95% CI: −1.59, −0.32). Improvements in Neuropathic Pain Scale composite score ($p = 0.007$), sleep NRS ($p = 0.001$), dynamic allodynia ($p = 0.042$), punctate allodynia ($p = 0.021$), Pain Disability Index ($p = 0.003$) and Patient's Global Impression of Change ($p < 0.001$) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication. Of all participants, 18% on sativex and 3% on placebo withdrew during the study. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks.

Keywords: Sativex; Cannabinoid; Peripheral neuropathic pain; Allodynia

1. Introduction

The treatment of chronic neuropathic pain is mainly pharmacological, with antidepressants, antiepileptic drugs, opioids and topical local anaesthetics constituting the first-line therapy [2]. Despite differences in their mechanism of action, these agents appear similar in analgesic efficacy and tolerability. There is a well-recognised need for better pain relief than is currently available. This study reports the effect of the administration of a highly standardised THC:CBD endocannabinoid system modulator, sativex (Sativex®), on the severity of pain and allodynia, and associated sleep disturbance, mental distress and disability in patients with peripheral

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neuropathic pain. Identification of cannabinoid receptors [20] and encouraging results from preclinical and clinical studies [15,16] and change in the political and scientific scene in some countries, notably Canada, have led to revived interest in cannabinoids as a therapeutic modality. Two controlled trials on central pain associated with MS found short-term efficacy from them [26,30], whereas two other studies in which pain was not a primary outcome measure gave conflicting results [33,40]. Neuropathic pain of peripheral or mixed peripheral and central origin was reported to respond to ajulemic acid, sativex or smoked cannabis; however, treatment arms in these studies were short, between 5 and 14 days [1,6,19].

Sativex is derived from extracts of selected strains of cannabis plants (*Cannabis sativa*) which produce high and reproducible yields of the principal active cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). It is administered as a spray for sublingual and oro-pharyngeal administration. Each 100 μl spray delivers 2.7 mg of THC and 2.5 mg of CBD.

Cannabinoids are thought to work via two types of receptors, CB1 and CB2. CB1 is widely distributed in the peripheral and central nervous system, acting as a presynaptic modulator of neurotransmitter release. The main target for the effects of THC, CB1, occurs at many sites critical for nociception. CB2 is also activated by THC but in normal circumstances is found in immune cells only. However, in clinical pain the role of the CB2 receptor may be different because following tissue injury it is shown to be expressed in central nervous system microglia and dorsal root ganglion cells following tissue injury [28] CBD appears to have limited affinity for either cannabinoid receptor, but in higher doses may potentiate the effects of THC [32] and mediate non-cannabinoid effects by activating the TRPV1 receptor [8]. Combining the two in the same preparation is thought to lead not only to increased analgesic effect but may also result in antagonism of adverse effects [27].

2. Methods

2.1. Study design

This was a 5-week multi-centre (5 centres in UK, 1 in Belgium), randomised, double-blind, placebo-controlled parallel group study. Patients were screened to determine eligibility and completed baseline diary assessments of daily pain intensity and sleep disturbance scores in the 7–10 days prior to first treatment assignment. After eligibility was confirmed, patients were assigned to the next sequential randomisation number within each centre. The randomisation schedule had a 1:1 treatment allocation ratio with randomly permuted blocks stratified by centre and was generated using a computer based pseudo-random number algorithm. The randomisation schedule was held by the sponsor with a copy in patient-specific sealed envelopes sent to the pharmacy in each centre. Once the patient's eligibility was confirmed, they were assigned to the next sequential randomisation number within each centre. The placebo medication was identical in composition, appearance, odour and taste with the study medication but without cannabis extract. That the smell and taste of the cannabinoid preparation might lead to unblinding was averted by disguising them with addition of peppermint oil to both preparations. All medication was provided in identical amber vials, packaged and labelled by the sponsor.

2.2. Study patients

Patients had to have a current history of unilateral peripheral neuropathic pain and allodynia. Further enrolment criteria are shown in Table 1. Concomitant analgesia was maintained at a stable dosage regimen for the duration of the study. The decision to recruit was based on the patient's history. No tests for drugs of abuse potential were carried out. Ethical approval was granted by the Local Ethics Committees of the participating centres. In one centre the approval was conditional on patients not driving during the trial.

2.3. Study medication and procedures

Initial dosing was under clinical supervision at the study site. A pre-dose 100 mm "Intoxication" (0 = no intoxication and 100 = extreme intoxication) Visual Analogue Scale (VAS) was obtained and vital signs were checked. A maximum of 8 sprays were administered over 2 h with Intoxication VAS and vital signs checked at regular intervals. If, following any dose, patients scored higher than 25 mm, or there were clinical concerns, e.g. the patients showing dysphoria or cardiovascular changes, subsequent doses were omitted [6,7].

After satisfactory completion of initial dosing, patients began home dose titration and were allowed a maximum dose of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. At the next visit (after 7–10 days) titration, compliance and adverse events were reviewed, and patients advised on how to optimise dosing for the rest of the study period. Those patients who satisfactorily completed the trial were offered the opportunity to participate in a common open-label extension study of sativex.

All used and unused study medication containers were returned at each visit to the research centre. Patients were withdrawn from the study if there were indications of misuse, including failure to record dosage accurately. Periodic telephone monitoring was undertaken at pre-arranged times during home dosing to check the patient's condition and to answer any queries. Throughout the study, allowable concomitant medications or treatments were continued to provide adequate background analgesia at a constant dose. Any medication, other than the study medication taken during the study, was recorded.

Patients kept a diary from the screening visit until end of treatment in which they recorded daily their pain and sleep scores (on the appropriate NRS), as well as adverse events and the number of sprays used.

Table 1
Enrolment criteria

Inclusion criteria	Exclusion criteria
Unilateral peripheral neuropathic pain and allodynia	Cannabinoid use (cannabis, Marinol® (synthetic THC) or nabilone (synthetic cannabinoid analogue)) at least 7 days before randomisation. Subjects were required to abstain from use of cannabis during the study
Age 18 or over, male or female	Schizophrenia, psychosis, or other major psychiatric condition beyond depression with underlying condition
A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion	Concomitant severe non-neuropathic pain or the presence of cancer related neuropathic pain or from diabetes mellitus
Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination	Known history of alcohol or substance abuse
Patients with complex regional pain syndrome (CRPS) were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II)	Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment
A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week	Scheduled surgery or anaesthesia
A stable medication regimen of analgesics for at least 2 weeks prior to study entry	Terminal illness or subjects inappropriate for placebo therapies
Female patients of child bearing potential and male patients whose partner was of child bearing potential had to agree to use effective contraception	Known hypersensitivity to cannabinoids
Willing for his or her name to be notified to the UK Home Office	Participation within a trial in the last 12 weeks

2.4. Testing for allodynia

Tests for allodynia were carried out at baseline and end of study. The investigator recorded the most painful area within the affected territory. Mechanical dynamic allodynia was assessed by stroking the skin over the affected area five times with a standardised brush, designed specifically for sensory testing (Senselab Brush-05, Somedic, Horby, Sweden) at $\geqslant$5 s intervals, and recording the pain severity on a 0–10 point scale. All strokes were of the same length, minimum 2 cm. Each dynamic allodynia score was calculated as the average of the five strokes.

Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). A contralateral mirror image site was used as control to identify any systemic effect from the trial drugs, as well as to introduce the method to the patient before performing the test on the allodynic site. This control site was checked for evidence of local injury, scar, rash or neurological deficit. During each session the normal contralateral side was tested first. Once the patient indicated that the sensation of pressure had turned into pain, the algometer was removed and the pressure reading (in grams) recorded. The same method was used for allodynic sites.

In addition, patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 (no pain) and 10 (most intense pain imaginable). The investigators were aware of the previous punctate allodynia threshold and could use it as guidance. Because some investigators expressed concern at using a rigid threshold as a targe for the second measurement, it was agreed that they could exercise discretion in applying the force needed to reproduce approximately the same pain as at baseline. The patients' verbal pain score and pressure used were recorded. Each punctate pain provocation test was done only once during a single visit.

2.5. Outcome measures

The primary outcome measure was a change from baseline on a numerical rating scale (NRS) of mean intensity of global neuropathic pain, where 0 = "No Pain" and 10 = "Worst Possible Pain". Secondary measures included the composite score calculated from the Neuropathic Pain Scale (NPS) [10], tests for mechanical allodynia, a four-step verbal rating scale for sleep disturbance (see below), the Pain Disability Index (PDI) [31], the Patient Global Impression of Change (PGIC) of both pain and allodynia, and the General Health Questionnaire (GHQ-12) [5]. Possible cognitive decline was assessed using the Brief Repeatable Battery of Neuropsychological tests (BRB-N) [7]. Information regarding the frequency of administration of the medication was recorded by the subjects in their diary. Adverse events were collected at each clinic visit, and haematology, clinical chemistry and ECG monitored at the beginning and end of the study.

2.6. Statistical analysis

The sample size calculation was based on an expected SD of 1.8 for the pain intensity score, estimated from several studies on peripheral neuropathic pain. To detect a difference between treatment groups of 1.0 on a 0–10 (11-point) NRS with 80% power and a 5% level of significance, 52 evaluable subjects per group were required. A dropout rate of 15% was anticipated, bringing the total number of patients needed to 120.

The primary analysis for the primary and secondary endpoints was performed on the intention-to-treat (ITT) population. The neuropathic pain intensity NRS score at baseline was defined as the mean of all diary entries from Day −7 to Day −1 and, for the end of treatment score, the mean of all diary entries during the last 7 days in the study, or the last 3 days in the event of withdrawal. The NRS scores were summarised by treatment group for baseline, each week and end of treatment. The change in NRS pain scores was compared between treatment groups using analysis of covariance, the model including treatment and trial centre as factors and baseline pain severity as a covariate. From this analysis the adjusted treatment means, treatment difference and 95% Confidence Interval (95% CI) for the treatment difference were calculated.

The total scores for all questionnaires (NPS, PDI, GHQ-12), as well as 0–10 NRS ratings of punctate and mechanical allodynia, were obtained at baseline and end of the 5-week trial. Sleep disturbance was measured by asking the subjects to indicate the number of times they woke in previous nights due to symptoms on a four category scale where 1 = none, 2 = once, 3 = twice, 4 = more than twice. The scores for this "Sleep Disturbance NRS" were obtained at baseline and weekly thereafter until the end of trial. Statistical comparisons were performed in the same way as the primary outcome measure. The PGIC was compared between treatments using Fisher's Exact Test.

3. Results

A total of 141 patients were assessed for eligibility, 16 (11%) of whom failed to meet the eligibility criteria. Sixty-three subjects were randomised to sativex and 62 to placebo (Fig. 1). At all participating centres, the randomisation led to a complete balance between treatment allocations. Baseline demographic details for both groups are shown in Table 2. The treatment groups were well matched for age, duration of neuropathic pain, distribution of diagnostic pain subgroups, height, weight and for history of previous cannabis use. The diagnosis was based on existing clinical, imaging and neurophysiological

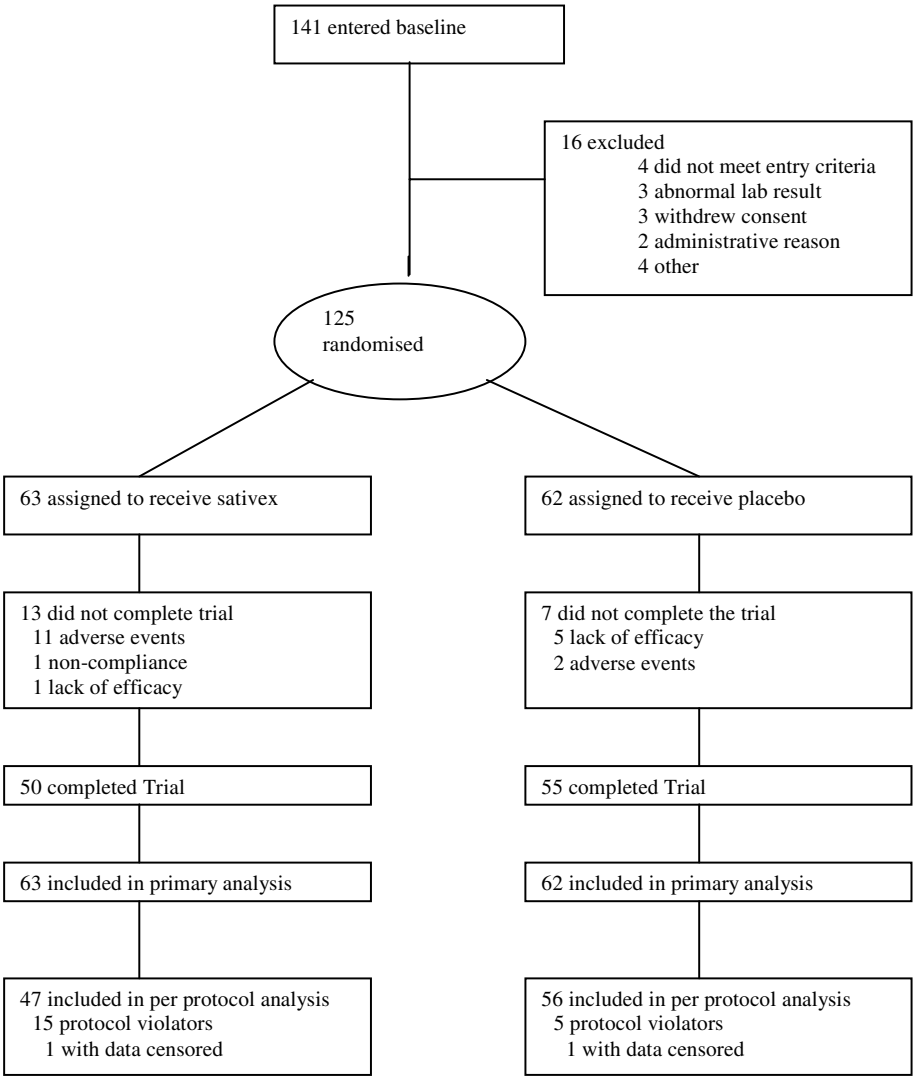

Fig. 1. Study flow.

Table 2
Patient characteristics

	Sativex ($N = 63$)	Placebo ($N = 62$)
Age, yr mean (SD)	52.4 (15.8)	54.3 (15.2)
Women, *N* (%)	35 (55.6)	39 (62.9)
White, *N* (%)	61 (97)	60 (97)
Weight, kg mean (SD)		
Men	79.9 (16.7)	86.8 (16.7)
Women	72.0 (18.2)	72.7 (17.3)
Duration of pain, yr mean (SD)	6.4 (5.7)	6.2 (6.4)
Underlying diagnosis		
Subjects (%)		
Postherpetic neuralgia	10 (16)	7 (11)
Peripheral neuropathy	13 (21)	12 (19)
Upper limb	2	1
Lower limb	5	4
Face/neck/trunk	6	7
Focal nerve lesion	26 (41)	28 (45)
Upper limb	8	7
Lower Limb	10	11
Face/neck/trunk	8	10
Radiculopathy	7 (11)	6 (10)
CRPS type II	7 (11)	8 (13)
Other	0 (0)	1 (2)
Prior cannabis use *N* (%)	13 (21)	12 (19)
Concomitant medication		
Subjects *N* (%)		
Antiepileptic	21 (33)	21 (34)
Tricyclic	16 (25)	21 (34)
Opioid	40 (63)	46 (74)
Strong[a]	7 (11)	8 (13)
Weak[b]	33 (52)	38 (61)
Analgesic, non-opioid	10 (16)	6 (10)
Anti-inflammatory	10 (16)	15 (24)
Pain NRS, mean (SD)	7.3 (1.4)	7.2 (1.5)
NPS composite score, mean (SD)	61.1 (13.0)	62.4 (13.7)
Dynamic allodynia NRS, mean (SD)	5.4 (2.7)	5.0 (3.4)
Punctate allodynia NRS, mean (SD)	7.3 (1.8)	7.4 (2.1)
Punctate allodynia, pressure g, mean (SD)	68.8 (47.7)	83.0 (77.4)
Pain Disability Index (PDI) mean (SD)	40.9 (14.7)	42.1 (13.4)
Sleep disturbance NRS, mean (SD)	3.0 (0.8)	3.0 (0.9)
GHQ-12, mean (SD)	17.2 (7.3)	17.6 (6.5)

[a] Morphine, methadone, oxycodone, pethidine.
[b] Tramadol, codeine, dihydrocodeine, dextropropoxyphene.

data. Aetiologies varied from post-infectious to traumatic, vascular and idiopathic. In nearly one-half of patients the cause was posttraumatic and involved a single nerve or nerve branch (focal nerve lesion) while in one-fifth the lesion was at cervical, brachial or lumbosacral plexus level or involved several nerves (peripheral neuropathy); in this group the original cause was either inflammation or diffuse trauma and remained frequently unknown. The locations of focal nerve lesions and peripheral neuropathics were similar across the two groups (Table 2). The background use of concomitant analgesic medication was high in both groups. The most frequently reported medication was opioids, being taken by 74% of the placebo group and 63% of the sativex group. Other frequently used background medications were tricyclic antidepressants, antiepileptic drugs, and NSAIDs (Table 2).

Thirteen sativex patients (21%) failed to complete the study; 11 withdrew because of side effects, 1 due to patient non-compliance and one due to lack of efficacy. Seven patients (11%) on placebo failed to complete the study, 2 because of adverse effects and 5 because of lack of effect. All randomised patients were included in the ITT analysis. For the per-protocol (PP) analysis, there were 47 patients on sativex and 56 on placebo. Protocol violations were due to failure to meet the stringent time window set for the final visits (12 patients on sativex, 2 on placebo), use of prohibited medication (6 on sativex, two of whom also failed to meet the final visit time window, and 2 on placebo) or violation of inclusion/exclusion criteria (0 on sativex, 2 on placebo). One patient in each group had their data censored because of use of prohibited medication after Day 26.

3.1. Primary outcome measure

At baseline, the mean intensity of reported pain scores (SD) on NRS was in the severe range with no difference between the sativex and placebo groups 7.3 (1.4) and 7.2 (1.5), respectively (Table 2). At the end of treatment, the sativex group demonstrated an adjusted mean change in NRS score of −1.48 points (a 22% reduction) while the change for the placebo group was −0.52 points (an 8% reduction) (Fig. 2). The estimated treatment

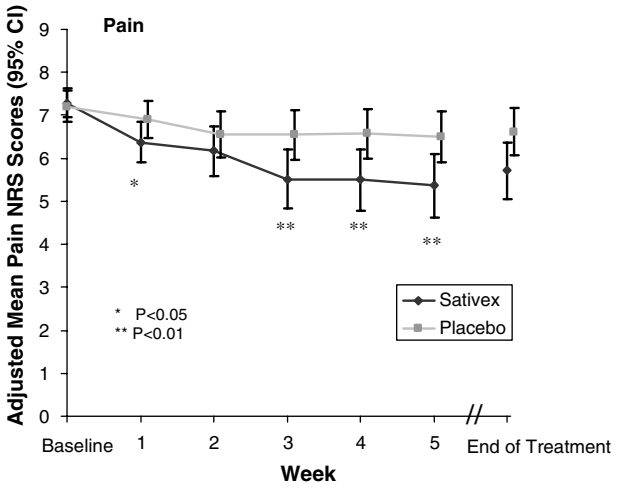

Fig. 2. Reduction of global neuropathic pain NRS scores in the two groups during the trial. First-week: home-titration; subsequent four weeks: maintenance therapy. Weekly mean pain scores were obtained from pain diaries. End-point scores were obtained from diary entries during the last 7 days, or last 3 days in case of withdrawal, for the ITT analysis. Error bars represent 95% confidence intervals.

difference of −0.96 points was statistically significant in favour of sativex ($p = 0.004$; 95% CI: −1.59, −0.32). The improvement in pain over placebo was evident from the second week after self-titration and was maintained until the end of the study (Fig. 2). On sativex, 26% of patients had at least a 30% reduction in pain score and 20% of patients had at least a 50% reduction in pain score, compared with 15% and 8% of patients on placebo; the NNT (50%) and NNT (30%) calculated from these figures were 8.5 and 8.6, respectively. Analysis of the PP population also showed a significant treatment difference of −1.42 points in favour of sativex ($p < 0.001$; 95% CI: −2.10, −0.74).

3.2. Secondary outcome measures

All questionnaire-based measures of pain and pain-related co-morbidity improved significantly more in patients randomised to sativex than placebo (Table 3). NPS composite score in the sativex group decreased significantly more than in the placebo group. Sleep disturbance also decreased early on and improvement was maintained until the end of the study (Fig. 3). Of the seven functional areas assessed in the PDI, only sexual activity failed to show a substantial improvement on sativex (Table 3).

3.3. Allodynia

3.3.1. Dynamic mechanical allodynia

All patients recruited into the study showed dynamic allodynia. There was no difference in detected mean (SD) allodynia pain scores between the two groups at baseline (5.4 (2.7) vs. 5.0 (3.4)). At the end of treatment, the mean reduction of dynamic allodynia was 20% in the sativex group, and 5% in the placebo group, with an estimated mean treatment difference of −0.82 ($p = 0.042$; 95% CI: −1.6, −0.03)) in favour of sativex. NNT for 30% reduction in the allodynia score was 9.2 and for 50% reduction 7.5.

3.3.2. Punctate allodynia

At baseline, all randomised patients except one on sativex showed punctate allodynia with clearly reduced thresholds in the affected area vs. contralateral control

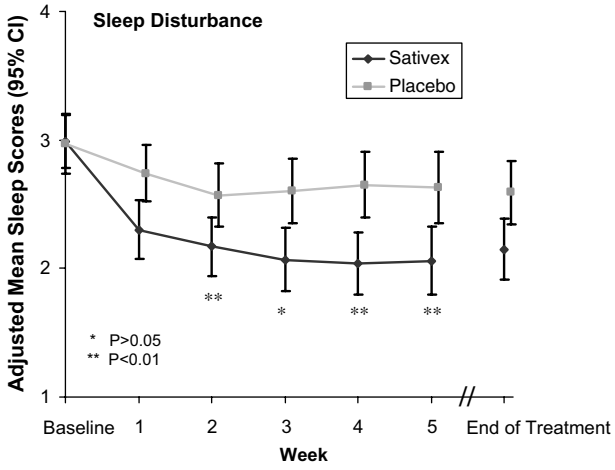

Fig. 3. Reduction is sleep disturbance scores in the two groups during the trial. For details, see text, and legend for Fig. 2.

(mean (SD) difference between the contralateral site and allodynic site: 127 (78) g). The severity of the allodynia within the affected area was comparable between both sativex and placebo groups for pressure needed to elicit pain (68.8 (47.7) g vs. 83.0 (77.4) g) and for the level of pain generated by the stimulus itself (7.3 (1.7) vs. 7.4 (2.1)). At the end of study, there was no evidence of a change in the punctate pain threshold at the contralateral control site, irrespective of whether the patients were on sativex or placebo (treatment difference 11.1 g in favour of placebo; $p = 0.3$). At the allodynic site, the placebo group reported unchanged punctate pain pressure thresholds at end of study (83.0 (77.4) g vs. 85.8 (68.9) g) with no change in pain levels (7.4 (2.1) and 7.2 (2.2)). In the sativex group, the threshold levels increased from 68.8 (47.7) g to 86.2 (73.2) g but not significantly compared to the placebo group ($p = 0.14$). Despite this increase of applied punctate pressure there was a notable decrease in the allodynia pain scores (baseline: 7.3 (1.7) vs. end of treatment: 6.2 (2.6)). The estimated treatment difference of −0.87 was in favour of sativex ($p = 0.021$; 95% CI: −1.62, −0.13), giving an NNT (30%) of 5.9 and NNT (50%) of 13.4.

Inspection of punctate allodynia data revealed that in some cases the pressure applied with the algometer to the allodynic site had changed considerably between

Table 3
Summary of the results of the secondary efficacy end-points (ITT analysis)

Secondary outcomes	Sativex	Placebo	Estimated mean difference (95% CI)[a]	*p*-Value
NPS composite score	−10.07	−2.04	−8.03 (−13.83, −2.23)	0.007
Sleep disturbance NRS	−0.79	−0.36	−0.43 (−0.67, −0.19)	0.001
Pain Disability Index (PDI)	−5.61	0.24	−5.85 (−9.62, −2.09)	0.003
Dynamic allodynia NRS	−1.18	−0.37	−0.82 (−1.60, −0.03)	0.042
Punctate allodynia NRS	−1.09	−0.21	−0.87 (−1.62, −0.13)	0.021
GHQ-12	−3.09	−2.34	−0.75 (−2.84, 1.35)	0.483
PGIC (all neuropathic pain)	51.61	19.35	32.26 (16.40, 48.12)	<0.001
PGIC (pain at allodynic site)	46.77	17.74	29.03 (13.79, 44.67)	0.001

[a] All treatment comparisons in favour of sativex.

pre-treatment and post-treatment. When a sensitivity analysis was carried out in patients in whom the investigators applied a similar degree of force (<5% greater) to the allodynic area on the second testing occasion (44 patients on sativex and 45 on placebo), there was a significantly larger reduction of allodynia pain in the sativex group than the placebo group leading to a treatment difference of −0.94 ($p = 0.046$; 95% CI: −1.85, −0.02) in line with the ITT analysis.

When all subjects were analysed together, there was a strong correlation between the intensity of punctate allodynia, dynamic allodynia and spontaneous pain at baseline and end of study, with similar strong correlations between the three parameters for change in scores (punctate allodynia vs. dynamic allodynia, $r = 0.526$, $p < 0.001$; punctate allodynia vs. pain $r = 0.369$; $p < 0.001$; dynamic allodynia vs. pain, $r = 0.436$, $p < 0.001$). Inspection of sativex and placebo groups separately showed that similar significant correlations were present, except for change in dynamic allodynia in the placebo group ($r = 0.065$, $p = 0.61$).

Results of the secondary efficacy end-points are summarised in Table 3. Thirty-two (51.6%) patients taking sativex compared to 12 (19.3%) taking placebo considered their primary condition to be very much, much or minimally improved ($p < 0.001$, Fisher's exact test). The odds ratio for achieving a better response on sativex than placebo, calculated from a logistic regression of the data, was 3.55 (95% CI: −7.61, −1.72) in favour of sativex. There was no difference between groups in the GHQ-12 score.

3.4. Dosing pattern

The mean (SD) number of sprays taken during the first week of dose titration for sativex and placebo was 7.3 (3.5) and 10.9 (3.9), respectively. From the second week onwards, the dose frequency remained stable in both treatment groups, with no tendency to increasing dose over the duration of the study. The number of sprays used daily in the placebo group was higher than in the sativex group (Table 4). Over the study period, patients randomised to sativex used a mean (SD) of 10.9 (6.8) sprays daily compared with 19.0 (8.3) by patients on placebo.

3.5. Adverse events and withdrawals

Fifty-seven (91%) patients in the sativex group experienced at least one adverse event (AE) during the course of the study compared with 48 (77%) patients in the placebo group. The most frequent AEs were central nervous system related or gastrointestinal. Most were observed at onset of treatment, and in the majority described as mild. However, 6 (10%) patients on sativex reported several gastrointestinal AEs (nausea, vomiting diarrhoea, constipation) with none on placebo reporting the same. Severe symptoms suggesting involvement of the nervous system were reported with sativex in 7 (11%) and placebo 5 (8%) cases. All reported gastrointestinal AEs combined irrespective of their severity were more common in the sativex group (31/63 (49%) than in the placebo group (20/62 (32%), $p = 0.003$, Fisher's exact test), whereas the nervous system AEs (33/63 vs. 23/62, $p > 0.10$) were not. One case of severe psychiatric AE was recorded on both groups (with sativex, emotional stress associated with paranoid thinking and with placebo, confusion) and 6 further mild-to-moderate ones in the sativex group as opposed to 3 in the placebo group; these were mainly mood related. AEs seen in 3 or more subjects are shown in Table 5 for all AEs and for those considered possibly related to treatment.

In the sativex group, 11 (18%) patients withdrew due to an AE compared with 2 (3%) in the placebo group. There was one transient ischaemic attack in the sativex group rated as a serious adverse event (SAE) and

Table 4
Summary of exposure to study medicine (number of sprays per day based on patient diary entries)

		Sativex ($N = 63$)	Number of patients remaining	Placebo ($N = 62$)	Number of patients remaining
Week 1	Mean (SD)	7.31 (3.54)	62	10.94 (3.90)	62
	Median (range)	6.64 (1.3–14.7)		11.14 (3.0–21.3)	
Week 2	Mean (SD)	12.46 (8.07)	58	20.08 (9.79)	61
	Median (range)	10.86 (1.6–42.7)		19.71 (2.3–47.9)	
Week 3	Mean (SD)	13.32 (8.30)	55	21.10 (10.79)	60
	Median (range)	11.43 (1.7–37.4)		20.07 (1.7–48.0)	
Week 4	Mean (SD)	12.86 (8.63)	53	22.23 (11.51)	57
	Median (range)	10.86 (2.0–39.0)		20.43 (1.7–48.1)	
Week 5	Mean (SD)	13.63 (8.65)	48	22.26 (11.68)	54
	Median (range)	12.64 (1.1–37.7)		19.93 (2.9–50.6)	
Overall	Mean (SD)	10.89 (6.81)		19.02 (8.32)	
	Median (range)	9.81 (1.3–31.4)		17.91 (2.4–41.5)	

Table 5
Treatment emergent adverse events (AEs) experienced by 3 or more subjects (~ 5%) receiving sativex compared with placebo and the % of subject who withdrew due to these AEs

Adverse event	Number (%) of patients experiencing AEs		Number (%) of patients who withdrew due to AE	
	Sativex ($N = 63$)	Placebo ($N = 62$)	Sativex ($N = 63$)	Placebo ($N = 62$)
Dizziness	18 (28.6)	9 (14.5)	2 (3.2)	0
Nausea	14 (22.2)	7 (11.3)	1 (1.6)	0
Fatigue	13 (20.6)	5 (8.1)	0	0
Dry mouth	11 (17.5)	3 (4.8)	0	0
Vomiting	8 (12.7)	3 (4.8)	2 (3.2)	0
Feeling drunk	6 (9.5)	1 (1.6)	1 (1.6)	0
Headache	6 (9.5)	9 (14.5)	0	0
Diarrhoea	4 (6.3)	0	2 (3.2)	0
Nasopharyngitis	4 (6.3)	2 (3.2)	0	0
Anorexia	4 (6.3)	0	1 (1.6)	0
Somnolence	4 (6.3)	1 (1.6)	0	1 (1.6)
Abdominal pain upper	3 (4.8)	1 (1.6)	0	0
Disturbance in attention	3 (4.8)	0	0	0
Memory impairment	3 (4.8)	0	0	0

considered unrelated to study treatment. Oral discomfort, other than dryness of mouth, occurred in 8 (13%) patients taking sativex and 11 (18%) taking placebo and was usually reported as mild. One patient on sativex had transient mucosal ulcerations but leukoplakia was not observed. No significant haematological or biochemical abnormalities were encountered in laboratory parameters.

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was given to 85 patients (43 randomised to sativex and 42 to placebo). No difference was seen between groups assessed for cognitive function with this method at the beginning and end of treatment (Table 6).

Intoxication scores (SD) remained low throughout the study, peaking after the self-titration week at 8.0 (15.4) for sativex and 3.0 (7.9) for placebo on a 0–100 scale, respectively. Five patients on sativex and 2 patients on placebo scored more than 40/100 during the maintenance period.

3.6. Long-term use of sativex

At the end of their 5-week trial period, each patient was offered the chance to enter an open-label extension study. Of the 125 subjects eligible, a total 89 (71%) of the patients accepted the offer. They subsequently underwent re-titration of sativex from zero, in a way identical to that used in the randomisation phase. Patients were reviewed initially at 4 weeks thereafter every 8 weeks.

The duration of participation in the extension trial ranged from 1 to 871 days. By study closure, 56 (63%) patients had been withdrawn; 18 patients due to adverse effects, 16 due to lack of efficacy, 15 due to withdrawal of consent, 7 for other reasons. The mean (SD) duration of the participation of withdrawn patients was 135 (147) days. An LOCF analysis involving 76 patients carried out at 52 weeks demonstrated a mean decrease of pain NRS from the baseline of 7.3 (1.4) to 5.9 (2.4), i.e., similar to that seen in the randomised trial. The daily number of sprays did not increase appreciably during this period (N (SD) 10.2 (6.0) at the end of the re-titration vs. 12.2 (7.6) at 52 weeks). Two episodes of serious adverse effects were reported (urticaria with eyelid oedema and an event of somnolence, dysarthria and weakness) both leading to withdrawal of the patient in question from the study.

4. Discussion

This study demonstrates that sativex is effective in the relief of peripheral neuropathic pain when given in addition to existing medication. Greater than 30% improvement in pain intensity, generally considered as clinically meaningful [9], was reported by 26% of subjects receiving sativex, compared with 15% of patients taking

Table 6
Psychomotor function during the trial shown as adjusted mean change from baseline in the BRB-N for each treatment group

Test	Sativex	N	Placebo	N	Difference	p-Value
Selective reminding	0.55	43	0.52	42	0.02	0.92
10/36 Spatial recall	0.85	43	0.31	42	0.53	0.21
Symbol digit modalities	1.48	43	3.63	42	−2.15	0.16
Paced serial addition	7.67	33	6.38	34	1.28	0.66
Word list generation	2.35	42	2.44	42	−0.08	0.96

No difference between groups (positive difference denotes better function on sativex and negative on placebo).

placebo. At recruitment, all our patients were either non-responders to several conventional neuropathic analgesics, or were in severe pain despite taking appropriate therapy. Considering the refractory nature of their pain, and that patients remained on their existing analgesia, the improvement of the ongoing pain in those on the active drug is encouraging. Further evidence for the efficacy of sativex comes from improvement in mechanical dynamic and punctate allodynia pain, sleep and disability demonstrated in this study. Reduction in systematically measured mechanical allodynia is not commonly reported in controlled trials on neuropathic pain [17] and usually only seen in single dose studies or following other than oral administration, and failure is common. [3,21,23,29,34–36]. Because to date there are no reliable data converting reduction in allodynia scores to clinically meaningful improvement, the NNT values presented should be interpreted with caution.

In comparison with pain relief reported from other cannabis-related clinical trials, sativex in our group of patients demonstrated a greater difference over placebo (0.96, 95% CI −1.59, −0.32) than in patients with plexus avulsion (treatment difference −0.58, 95% CI −0.98, −0.18) but somewhat less than in patients with central pain due to MS (−1.25; 95% CI −2.11, 0.39) [6,26]. The treatment difference reported for dronabinol in MS patients deprived of concomitant analgesic medication was 0.6 (95% CI −1.8, 0) while that for smoked cannabis in painful HIV neuropathy was approximately the same as in the present study (as extrapolated from the reported median 18% treatment difference in pain relief from mean baseline scores of 53 and 54/100) [1,30]. Differences in patient populations, numbers of withdrawals, concomitant medications, trial designs and trial durations probably explain a great deal of these varying results. Interestingly, the two other cannabinoid trials in which evoked pain was assessed, albeit in a limited fashion, also report some benefit in line with the present study [1,30].

Our reason for maintaining existing analgesia was based on both ethical and clinical considerations. A number of treatments that have shown efficacy in peripheral neuropathic pain are in widespread use in accordance with existing guidelines [2]. Depriving a patient from such therapies during a placebo-controlled trial could not be ethically justified. Clinical practice is also moving toward combination therapies due to the realisation that in chronic neuropathic pain multiple mechanisms are the norm [12,39].

The lack of GHQ-12 to show any change during the present study is in line with virtually all other cannabinoid trials in which the psychosocial domain was explored, irrespective of the measure used (GHQ-30, [40]; GHQ-28, [33]; SF-36, [30]; GHQ-12, [6]; HADS, [26]; POMS, [1]). GHQ-12 is a well-validated measure of anxiety, depression and social dysfunction [37] and shows adequate sensitivity to change in longitudinal studies in manifest depression [11]. The role of the endocannabinoid system in the regulation of anxiety and mood disorders still remains unclear, and both CB1 agonists and antagonists have been shown to possess either anxiolytic or anxiogenic effects as well as variable effects on mood [38]. It is possible that GHQ-12 cannot detect modest changes in a population such as ours scoring just above the mean of the general population [24]. Alternatively, the above paradoxical effects of THC, or the ability of CBD to block some of the psychomimetic effects of THC, may explain the lack of change in this measure.

The self-titration schedule used in this study was chosen for several reasons. Previous studies [6,26] indicated that individual subjects have a variable threshold to the known pharmacodynamic effects of sativex. A self-titration regimen permitted individual patients to optimise their dose on the basis of their own efficacy and tolerability response. Both experimental and human volunteer studies suggest that tolerance to some of the side effects of cannabis occurs within days of its repeated administration [14,18,22]. A self-titration regimen allows for this to occur, further optimising the therapeutic response. There appears to be substantial between-patient variability in the pharmacokinetics of THC and other cannabinoids [13,14] and in such circumstances the implementation of a fixed-dose regimen is likely to yield suboptimal results.

The mean number of sprays taken daily by the sativex group remained stable during the course of the study despite patients having the freedom to determine their own dosing, indicating that tolerance did not develop at least over the 4-week stable treatment period of this study. The dose titration regimen used was usually successful in providing the optimal therapeutic level for individual patients. This conclusion is endorsed by the observation that those patients who took part in the open-label extension study did not increase the number of daily sprays during the first 52 weeks of open-label treatment while apparently maintaining the initial analgesic effect.

While the therapeutic effects of cannabis have often been attributed to THC, the second major constituent of the trial medication, CBD has been shown to have effects which may be additive to those of THC in pain relief in animal models, and also to have the potential to ameliorate some of the psychoactive effects of THC [27]. This interaction between the two components may permit subjects to tolerate mean daily doses of more than 27 mg THC. This dose is in excess of those used in other controlled studies of THC, and may account for the observed efficacy [14].

The adverse events reported by the patients were mostly gastrointestinal, central nervous system related or topical. While reported gastrointestinal AEs were more common in the sativex group, central nervous sys-

tem AEs were not; and, importantly, objective measurement of psychomotor performance did not vary across the two groups. In general, the number of patients who withdrew is similar to those reported in well-known large trials of other drugs used in neuropathic pain [4,25]. That PCIG scores favoured sativex over placebo suggests that subjective pain relief, reduced disability and improved sleep overrode the negative impact of AEs.

There was no formal assessment of whether unblinding might have taken place. The psychotrophic effects of cannabis are well known to the public, and 20% of the participants in the present trial had previous exposure to cannabis. A post-hoc analysis found that previous use of cannabis was not predictive of the change in mean pain scores. Classical psychotrophic effects of cannabis were reported by relatively few patients. The intoxication scores were marginally higher in the sativex group, and psychometric tests (BRB-N) remained unchanged during the trial. It is therefore unlikely that a significant number of those on sativex would have correctly guessed they were on active medication unless they deliberately overdosed. From returned trial medication it was concluded that such practice did not take place. Patients taking placebo may have concluded that they were taking inactive substance, given that they used a relatively high number of sprays. However, the majority of patients took less than the highest allowable dosage. Also, only 5 (8%) of the placebo group withdrew for lack of efficacy, suggesting that no significant unblinding took place.

We conclude that the results from this study indicate that sativex has a positive broad spectrum therapeutic effect in neuropathic pain, when used in addition to existing analgesic medication. The emergence of a highly standardised, uniform preparation of THC:CBD should allow for further studies which better define the role for cannabinoids in the treatment of neuropathic pain syndromes.

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GW Pharma acted as the sponsor of the study, provided the medication, participated in the study design, co-ordinated the study between centres and carried out the first set of analyses. The analyses were verified by an independent statistician. The principal investigator had full access to all the data and carried out further confirmatory analyses. All authors contributed to the study design, collection of the data and interpretation of the results. The editorial content of this paper is of the authors, as is the final decision to submit for publication.

References

[1] Abrams DI, Jay CA, Shade SB, Vizoso RN, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy. A randomised placebo-controlled trial. Neurology 2007;68:515–21.

[2] Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006;11:1153–69.

[3] Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology 2004;62:218–25.

[4] Backonja MA, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831–6.

[5] Banks MH. Validation of the General Health Questionnaire in a young community sample. Psychol Med 1983;13:349–53.

[6] Berman JS, Symonds C, Birch R. Efficacy of cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Pain 2004;112:299–306.

[7] Bever Jr CT, Grattan L, Panitch PH, Johnson KP. The Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis: a preliminary serial study. Mult Scler 1995;1:165–9.

[8] Costa B, Giagnoni G, Franke C, Trovate AE, Colleani M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol 2004;143:247–50.

[9] Farrar JT, Young JP, La Moreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2000;94:149–58.

[10] Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology 1997;48:28–33.

[11] Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med 1997;27:191–7.

[12] Gilron I, Bailey JM, Tu D, Holder R, Weaver DF, Houlder RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324–34.

[13] Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing pharmacokinetic effects, pharmacokinetic characteristics and cognitive profiles of as single dose of three formulations of cannabis based medicine extracts (CBMEs) plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes. J Cannab Ther 2003;3:35–77.

[14] Guy GW, Robson P. A Phase I, a double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers. J Cannab Ther 2003;3:121–52.

[15] Herzberg U, Eliav E, Bennett GJ, Kopin IJ. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neurosci Lett 1997;221:157–60.

[16] Iskedijan M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis pain. Curr Med Res Opin 2007;23:17–24.

[17] Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. Eur J Pain 2002;6(Suppl A):618.

[18] Jones RT. Cardiovascular system effects of marijuana. J Clin Pharmacol 2002;42:58S–63S.

[19] Karst M, Salim K, Burstein S, Conrad I, Hog C, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain. JAMA 2003;290:1757–62.

[20] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4.

[21] Meier T, Wassner G, Faust M, Kuntzner T, Ochsner F, Hueppe M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Pain 2003;106:151–8.

[22] Nahas GG, Schwartz IW, Adamec JM, Manger WM. Tolerance of delta 9 THC in the spontaneously hypertensive rat. Proc Soc Exp Biol Med 1973;142:58–60.

[23] Nikolasjen L, Gotrup H Kristensen AG, Jensen TS. Memantine (a *N*-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: a randomized, double-blind, cross-over study. Anesth Analg 2000;91:960–6.

[24] Pevalin DJ. Multiple applications of the GHQ-12 in a general population sample: an investigation of long-term retest effects. Soc Psychiatry Psychiatr Epidemiol 2000;35:508–12.

[25] Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double-blind, placebo-controlled study. Pain 2001;94:215–24.

[26] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized Controlled Trial of Cannabis Based Medicine in Central Neuropathic Pain due to Multiple Sclerosis. Neurology 2005;65:812–9.

[27] Russo EB, McPartland JM. Cannabis is more than simply Delta(9)-tetrahydrocannabinol. Psychopharmacology (Berl) 2003;165:431–2.

[28] Sagar DR, Kelly S, Millns PJ, O'Shaughnessey CT, Kendall DA, Chapman V. Inhibitory effects of CB_1 and CB_2 receptor agonists on responses of DRG neurons and dorsal horn neurons in neuropathic rats. Eur J Neurosci 2005;22:371–9.

[29] Serpell MG. Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndrome: a double-blind, placebo-controlled trial. Pain 2002;99:557–66.

[30] Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. Br Med J 2004;329:25–38.

[31] Tait RC, Chibnall JT, Krause S. The Pain Disability Index: psychometric properties. Pain 1990;40:171–82.

[32] Varvel SA, Wiley JL, Yang R, Bridgen DT, Lomg K, Lichtman AH, et al. Interactions between THC and cannabidiol in mouse models of cannabinoid activity. Psychopharmacology 2006;186:226–34.

[33] Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects in multiple sclerosis? A double-blind, randomised, placebo-controlled study on 160 patients. Mult Scler 2004;10:434–41.

[34] Wallace M, Braun J, Schulters G. Postdelivery of alfentanil and ketamine has no effect on intradermal capsaicin induced pain and hyperalgesia. Clin J Pain 2002;18:373–9.

[35] Wallace MS, Magnusson S, Ridgeway B. Efficacy of oral mexiletine for neuropathic pain: a double-blind, placebo-controlled, cross-over study. Reg Anesth Pain Med 2000;25:459–67.

[36] Wallace MS, Rowbotham MC, Katz NP, Dworkin DH, Dotson RM, Galer BS, et al. A randomized, double-blind, placebo-controlled trial of glycine antagonist in neuropathic pain. Neurology 2002;59:1694–700.

[37] Werneke U, Goldberg DP, Yalsin I, Ustun BT. The stability of the factor structure of the General Health Questionnaire. Psychol Med 2000;30:823–9.

[38] Witkin JM, Tzavara ET, Nomikos GG. A role for cannabinoid CB1 receptors in mood and anxiety disorders. Behav Pharmacol 2005;16:315–31.

[39] Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci 2004;74:2605–10.

[40] Zajisec J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003;363:1517–26.

CONSENSUS STATEMENT

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

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DE Moulin, A Boulanger, AJ Clark, et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19(6):328-335.

BACKGROUND: Neuropathic pain (NeP), redefined as pain caused by a lesion or a disease of the somatosensory system, is a disabling condition that affects approximately two million Canadians.
OBJECTIVE: To review the randomized controlled trials (RCTs) and systematic reviews related to the pharmacological management of NeP to develop a revised evidence-based consensus statement on its management.
METHODS: RCTs, systematic reviews and existing guidelines on the pharmacological management of NeP were evaluated at a consensus meeting in May 2012 and updated until September 2013. Medications were recommended in the consensus statement if their analgesic efficacy was supported by at least one methodologically sound RCT (class I or class II) showing significant benefit relative to placebo or another relevant control group. Recommendations for treatment were based on the degree of evidence of analgesic efficacy, safety and ease of use.
RESULTS: Analgesic agents recommended for first-line treatments are gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors. Tramadol and controlled-release opioid analgesics are recommended as second-line treatments for moderate to severe pain. Cannabinoids are now recommended as third-line treatments. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol and botulinum toxin. There is support for some analgesic combinations in selected NeP conditions.
CONCLUSIONS: These guidelines provide an updated, stepwise approach to the pharmacological management of NeP. Treatment should be individualized for each patient based on efficacy, side-effect profile and drug accessibility, including cost. Additional studies are required to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes and treatment of pediatric, geriatric and central NeP.

Key Words: *Analgesic agents; Neuropathic pain; Randomized controlled trials*

La prise en charge pharmacologique de la douleur neuropathique chronique : une déclaration de consensus révisée de la Société canadienne de la douleur

HISTORIQUE : La douleur neuropathique (DNe), redéfinie comme une douleur causée par une lésion ou une maladie du système somatosensoriel, est un trouble invalidant dont sont affligés environ deux millions de Canadiens.
OBJECTIF : Examiner les essais aléatoires et contrôlés (EAC) et les analyses systématiques liées à la prise en charge pharmacologique de la DNe pour préparer une déclaration de consensus révisée, fondée sur des faits probants, à l'égard de sa prise en charge.
MÉTHODOLOGIE : Les EAC, les analyses systématiques et les lignes directrices sur la prise en charge pharmacologique de la DNe ont été évaluées lors d'une réunion de consensus en mai 2012, puis mises à jour en septembre 2013. Les médicaments étaient recommandés dans le document de consensus si leur efficacité analgésique était soutenue par au moins une EAC solide sur le plan méthodologique (classe I ou II), qui démontrait des avantages marqués par rapport à un placebo ou à un autre groupe témoin pertinent. Les recommandations thérapeutiques reposaient sur la qualité des preuves d'efficacité analgésique, d'innocuité et de facilité d'utilisation.
RÉSULTATS : Les analgésiques recommandés pour le traitement de première intention sont les gabapentinoïdes (gabapentine et prégabaline), les antidépresseurs tricycliques et les inhibiteurs spécifiques du recaptage de la sérotonine et de la noradrénaline. Le tramadol et les opioïdes à libération contrôlée sont recommandés en deuxième intention pour la douleur modérée à grave. Les cannabinoïdes sont désormais recommandés en troisième intention, tandis que la méthadone, les anticonvulsivants dont l'efficacité est moins attestée (p. ex., lamotrigine, lacosamide), le tapentadol et la toxine botulique sont recommandés en quatrième intention. Certaines polythérapies analgésiques sont acceptées pour traiter des troubles de DNe particuliers.
CONCLUSIONS : Ces lignes directrices fournissent une démarche mise à jour et graduelle pour la prise en charge pharmacologique de la DNe. Le traitement devrait être personnalisé en fonction de chaque patient, compte tenu de l'efficacité, du profil d'effets secondaires et de l'accessibilité du médicament, y compris son coût. D'autres études s'imposent pour faire des comparaisons directes entre analgésiques et examiner des combinaisons d'analgésiques, les résultats à long terme et le traitement de la DNe en pédiatrie, de la DNe en gériatrie et de la DNe centrale.

Neuropathic pain (NeP) has been redefined as pain caused by a lesion or a disease of the somatosensory system, and may be generated by either the peripheral or central nervous system, or both (1). Pain may be a manifestation of nerve injury, but there are few predictors to indicate which patients will develop this complication. For example, 50% of diabetic patients develop neuropathy during the course of their illness, but only approximately 15% report actual dysesthesias or pain (2). Similarly, breast surgery with transection of the intercostal brachial nerve results in NeP in up to 50% of patients (3). Previous prevalence estimates indicated that 2% to 3% of the population in the developed world experience NeP (4,5). However, newer studies using population-based questionnaires estimate a higher rate of 4% to 8% (6,7), which suggest that approximately two million Canadians experience this disabling condition. Even more striking is that the prevalence of NeP is likely to increase for a number of reasons. The population is aging, and a pandemic of obesity is occurring in the developed world. These factors are largely responsible for increasing rates of postherpetic neuralgia and painful diabetic neuropathy (8,9). In addition, survival rates are increasing among cancer patients, and many of the medical and surgical interventions used in the treatment of cancer (including chemotherapy) can cause NeP (10).

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METHODS

In 2007, the Canadian Pain Society (CPS) produced the first guidelines on pharmacological management of NeP tailored to the clinical practices of Canadian health professionals including analgesic agents specifically available in Canada (11). A consensus meeting was held in Whistler, British Columbia under the direction of the Neuropathic Pain Special Interest Group of the CPS in May 2012 to update these guidelines, given the plethora of systematic reviews and meta-analyses published since 2007 (Appendix A). There is also recent evidence from community-based studies that management of NeP, including postherpetic neuralgia, is not consistent with evidence-based recommendations (12). Funding for this consensus meeting was provided by the Neuropathic Pain Special Interest Group of the CPS. This involved a multidisciplinary group of individuals with research and clinical expertise relevant to the pathophysiology and management of NeP. This group met to review the randomized controlled trials (RCTs) and systematic reviews related to the pharmacological management of NeP to develop a revised evidence-based consensus statement on the management of NeP (13). Subsequent literature was reviewed by the group until September 2013.

Systematic searches on Medline and Cochrane databases were conducted to identify recent systematic reviews, meta-analyses and treatment recommendations, guidelines and/or consensus statements published since the first 2007 CPS consensus statement. Other selected publications and references were also considered. Medications could be recommended in the consensus statement if their analgesic efficacy was supported by at least one methodologically sound RCT (class I or class II) showing significant benefit relative to placebo or another relevant control group. Trials were excluded if they represented uncontrolled studies, had sample sizes of <10 patients or studied cancer NeP except for well-defined postsurgical pain syndromes (eg, postmastectomy pain syndrome) and chemotherapy-induced NeP. Trials were also excluded if they studied trigeminal or glossopharyngeal neuralgia because these conditions have their own specific medical and surgical treatments (14). The initial draft of the present manuscript was prepared by the first author and subsequent revisions were based on feedback from the other authors until consensus was achieved.

The current guidelines are based on quality of evidence of analgesic efficacy, side-effect profiles and ease of use. Medications were considered to be first line if there was high-quality evidence of efficacy (at least one class I study or two consistent class II studies – level of recommendation grade B or better) (15); positive results in at least two NeP models (16); and if they were considered to be straightforward and of sufficient tolerability to prescribe and monitor. Medications were considered to be second or third line if there was high-quality evidence of efficacy, but the medication required more specialized follow-up and monitoring. Fourth-line treatments had at least one positive RCT, but require further study. A limitation of this algorithmic classification is that grading of tolerability and ease of use was based solely on consensus opinion of the authors.

Target users for these guidelines are physicians, nurse practitioners and other allied health care individuals involved in the management of NeP. These guidelines have been endorsed by the Canadian Pain Coalition, an advocacy group for patients living with chronic pain. The published guidelines will be disseminated through various websites, including the CPS website, and reprints will be made available to undergraduate and postgraduate trainees, and practicing health care workers attending continuing medical education events. They will be updated periodically by the Neuropathic Pain Special Interest Group of the CPS.

CLINICAL CHARACTERISTICS AND DIFFERENTIAL DIAGNOSES OF NeP

The clinical features of NeP can be divided into spontaneous pain and stimulus-evoked pain. Spontaneous pain is commonly described as burning or intense tightness with superimposed shooting or lancinating pain. Stimulus-evoked pain includes allodynia, defined as painful sensations in response to a normally nonpainful stimulus, and hyperalgesia, defined as increased pain sensitivity in response to a normally painful stimulus. Superimposed autonomic features, such as alterations in temperature, colour and sweating as well as the development of trophic changes, suggest a diagnosis of reflex sympathetic dystrophy or complex regional pain syndrome (17).

The differential diagnosis of NeP is extensive and includes central and peripheral causes. Examples of central NeP include poststroke pain ('thalamic pain syndrome'), pain related to multiple sclerosis and pain due to spinal cord injury. Common causes of peripheral NeP include painful diabetic neuropathy, postherpetic neuralgia and surgically induced NeP, following thoracotomy, amputation, breast surgery and back surgery sometimes associated with nerve root fibrosis.

The diagnosis of NeP is based primarily on the patient's history and physical examination. Postherpetic neuralgia and painful diabetic neuropathy are typically easy to diagnose when there is a history of shingles and diabetes mellitus, respectively. However, pain radiating into an extremity can be either referred myofascial pain or NeP, and these can be much more challenging to diagnose. Simple questionnaires based on sensory descriptors and sensory examination have been developed to differentiate between somatic pain and NeP. Instruments such as the *Douleur Neuropathique 4* and the Leeds Assessment of Neuropathic Symptoms and Signs have been shown to be valid and reliable discriminators of NeP (18,19). In addition, the presence of true weakness (sometimes difficult to differentiate from pain-related or antalgic weakness), reduced or absent reflexes, allodynia and hyperalgesia all favour a diagnosis of NeP. Electromyography and nerve conduction studies are sometimes useful to provide more objective evidence of nerve injury, although electromyography study results are often normal in small-fibre neuropathies. Guidelines are available to determine the diagnostic certainty of NeP (possible, probable or definite) based on history, sensory signs, neurophysiological testing and neuroimaging (1).

GENERAL CONSIDERATIONS

Because NeP can be severe and unrelenting, it is important to recognize and treat comorbidities such as anxiety and depression. It is also important to recognize secondary treatment goals such as improving sleep, ability to function and overall quality of life. However, treatment goals must be realistic. Caregivers should validate the patient's pain to gain their trust and should set realistic treatment goals. This is typically straightforward from the caregiver's point of view because most NeP states are based on well-defined injuries to the nervous system. The primary goal in most cases is to make the pain 'bearable' or 'tolerable' – not to eliminate the pain. Such goal setting can make a considerable difference in patient satisfaction when pharmacological treatments are instituted.

Due to the lack of head-to-head trials to guide treatment choices, one approach to estimate the relative efficacy of analgesic agents in RCTs is to use the number needed to treat (NNT) – the number of patients that need to be treated with a certain drug to provide one additional patient with at least 50% pain relief relative to the comparator group. The NNT is used to estimate treatment efficacy, recognizing that there are limitations to this methodology including variability in RCTs (eg, crossover versus parallel design) and the short-term nature of most RCTs. Another approach to estimate efficacy is to determine the effect size – defined as the mean difference between active agent and placebo divided by the SD. The effect size can be classified as small (<0.5), medium (0.5 to <0.8) or large (≥0.8) (20).

Appendix A summarizes the results of a systematic search of systematic reviews, meta-analyses and treatment recommendations, guidelines and/or consensus statements published since the first 2007 CPS consensus statement. These results were reviewed and approved by two coauthors (DEM and IG) and provide the basis for the consensus statement presented here.

FIRST-LINE ANALGESICS

Two classes of medications are recommended for first-line treatment in the management of NeP – anticonvulsants and certain antidepressants.

Anticonvulsants

The gabapentinoids, gabapentin and pregabalin, bind to presynaptic voltage-gated calcium channels in the dorsal horn, reducing the release of excitatory neurotransmitters such as glutamate and substance P (21). These agents have been studied in large clinical trials, although mainly in the management of painful diabetic neuropathy and postherpetic neuralgia. Gabapentin has shown efficacy in three trials involving painful diabetic neuropathy and two trials involving postherpetic neuralgia (22); however, four RCTs involving gabapentin have been negative, including a trial of gabapentin in chemotherapy-induced painful neuropathy (23-26). The combined NNTs for gabapentin in the management of painful polyneuropathy and postherpetic neuralgia were 6.4 and 4.3, respectively (27).

Pregabalin is an analogue of gabapentin, with the same mechanism of action, but it manifests linear pharmacokinetics and has higher affinity for the presynaptic calcium channel. Four studies have shown that pregabalin provides significant pain relief and improved quality of life in painful diabetic neuropathy (28) and an additional four trials have shown efficacy in postherpetic neuralgia (22). The combined NNTs for pregabalin in the management of painful diabetic neuropathy and postherpetic neuralgia were 4.5 and 4.2, respectively (27). Pregabalin has also been studied in chronic central NeP following spinal cord injury, with evidence of significant pain relief (29,30). However, a study investigating pregabalin in the treatment of NeP associated with chronic lumbosacral radiculopathy was negative (31), as was a recent trial involving refractory painful diabetic neuropathy (32). A study investigating the safety and efficacy of pregabalin in patients with central poststroke pain showed no significant improvement in the primary end point of pain intensity; however, there were some improvements in secondary end points including sleep and anxiety (33).

Carbamazepine remains the drug of first choice for tic douloureux (idiopathic trigeminal neuralgia), but otherwise is not recommended for the management of NeP (14). Anecdotally, it may also be useful in the management of glossopharyngeal neuralgia (14).

Antidepressant agents

The tricyclic antidepressants (TCAs) have been shown to provide significant pain relief in various NeP conditions in many clinical trials, although the sample sizes have tended to be relatively small and most of these trials have used a crossover design (34). The combined NNTs for TCAs in the management of painful diabetic neuropathy and postherpetic neuralgia were 2.1 and 2.8, respectively (27).

The serotonin noradrenaline reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have mainly been studied in painful diabetic neuropathy. Duloxetine has demonstrated significant pain relief relative to placebo in three RCTs (28), with a combined NNT of 5.0 (27). A recent study investigating duloxetine in the management of chemotherapy-induced painful peripheral neuropathy showed a significant reduction in pain intensity relative to placebo, with a moderate effect size of 0.51 (35). However, duloxetine has also been studied in patients with central NeP due to spinal cord injury or stroke, and the results of this trial were negative (36).

Venlafaxine has shown efficacy in trials involving painful diabetic neuropathy (37) and mixed painful polyneuropathy (38) at doses of 150 mg to 225 mg daily. However, the latter trial, comparing venlafaxine with imipramine, showed a higher proportion of responders in the venlafaxine group. Another trial investigating venlafaxine plus gabapentin in the management of painful diabetic neuropathy showed significant pain relief relative to placebo plus gabapentin (39).

SECOND-LINE ANALGESICS

Two opioid-type medications are recommended for second-line treatment in the management of NeP.

Tramadol

Tramadol is a weak opioid agonist and mimics some of the properties of the TCAs in that it inhibits reuptake of noradrenalin and serotonin (40). Tramadol has shown significant benefit in three RCTs investigating painful diabetic neuropathy and mixed NeP syndromes, and has an overall NNT of 4.9 (27). Tramadol leads to less constipation and nausea than other weak opioid analgesics, such as codeine (41), but is more expensive in Canada. Tramadol should be used with caution in conjunction with selective serotonin reuptake inhibitors (SSRIs) because of increased risk of confusion and serotonin syndrome, especially among elderly patients (42).

Opioid analgesics

A recent meta-analysis of opioids for chronic noncancer pain included 16 randomized trials for chronic NeP (43). Most of these trials investigated painful diabetic neuropathy and postherpetic neuralgia; however, other trials focused on postamputation pain, sciatica and spinal cord injury pain. The authors found that opioids were more effective than placebo, with a moderate effect size (0.56) for pain. There was a small effect size (0.24) in favour of opioids for function in 13 of these RCTs. The combined NNT for opioids in the management of painful polyneuropathy and postherpetic neuralgia was 2.6 (27).

THIRD-LINE ANALGESICS

One class of medication is recommended for third-line treatment in the management of NeP – cannabinoids.

Cannabinoids

The cannabinoids are analgesic agents with increasing evidence of efficacy in central NeP states, with a combined NNT of 3.4 (27). Dronabinol produced modest analgesia in a trial investigating central pain in multiple sclerosis (44). A 50/50 mixture of tetrahydrocannabinol and cannabidiol in the form of an oral mucosal spray provided significant benefit in another trial investigating central pain in multiple sclerosis (45). A recent systematic review of clinical trials investigating cannabinoids in chronic pain determined that, since 2006, there have been seven high-quality (class I and II) studies investigating NeP, and all of these studies except one were positive (46). Four of these studies involved smoked cannabis for the management of HIV neuropathy (two studies), posttraumatic or postsurgical NeP, and combined central and peripheral NeP states. Two trials involved the cannabinoid oral mucosal spray in the management of multiple peripheral NeP states with allodynia and painful diabetic neuropathy. The single negative trial compared the synthetic cannabinoid nabilone with dihydrocodeine in peripheral NeP conditions, and found that dihydrocodeine was superior to nabilone. A more recent trial found that nabilone was effective in relieving symptoms of painful diabetic neuropathy, and also improved disturbed sleep and overall quality of life using an enriched enrollment withdrawal design (47).

FOURTH-LINE ANALGESICS

Several classes of medications can be considered to be fourth-line treatments for NeP – SSRIs, other anticonvulsants, methadone, topical lidocaine and miscellaneous agents.

SSRIs

SSRIs appear to have a weak analgesic effect in the management of NeP. Citalopram (48), paroxetine (49) and escitalopram (50) have been found to be efficacious in the management of painful diabetic neuropathy and painful polyneuropathy independent of their antidepressant effects, but fluoxetine has not (51). However, the combined NNT for all four studies was 6.8 (27). SSRIs used primarily for depression may inhibit the metabolism of TCAs and may increase the risk for serotonin syndrome (52).

Other anticonvulsants

Lamotrigine has been studied in a variety of peripheral and central NeP conditions, with variable results. Four studies investigating painful diabetic neuropathy, two studies investigating mixed NeP and single studies investigating chemotherapy-induced NeP and spinal cord injury pain were negative. Positive trials investigating HIV-related neuropathy, trigeminal neuralgia and central poststroke pain were reported; however, the sample sizes tended to be small, with significant dropout rates (53).

Lacosamide is an anticonvulsant agent with sodium channel-blocking properties. Lacosamide has been studied in five RCTs investigating painful diabetic neuropathy. There was modest benefit in each trial, with an NNT in the range of 10 to 12. Lacosamide, therefore, has limited efficacy in the treatment of painful diabetic neuropathy (54).

Topiramate and valproic acid have produced mixed results in NeP trials (27).

Methadone

Methadone is a synthetic opioid analgesic that may be useful in the management of NeP related to its *N*-methyl-D-aspartate antagonist properties (55). Two small RCTs demonstrated benefit from methadone in chronic NeP (56,57) and survey data suggested efficacy in mixed NeP conditions (58). Methadone has excellent oral bioavailability and a duration of action of at least 8 h with repetitive dosing. It has an elimination half-life of 24 h to 36 h, which requires close observation during the titration phase. There are no high-quality RCTs to support the use of methadone in the management of NeP, although guidelines for the use of methadone in the management of chronic pain are available (59). An RCT comparing methadone with other oral opioids is urgently needed.

Topical lidocaine

Topical lidocaine, as a sodium channel blocker, may be useful in the management of NeP. Systemic side effects are extremely rare as a result of negligible blood levels (60). Topical lidocaine is most practical for patients with localized peripheral NeP, such as postherpetic neuralgia, and remains a second-line agent for this condition based on three positive RCTs investigating lidocaine patch 5% in the management of postherpetic neuralgia (27). However, recent trials of lidocaine cream or patch 5% failed to provide benefit in patients with postsurgical peripheral nerve injury (61) or in mixed NeP (62). Therefore, there are conflicting results among placebo-controlled trials investigating topical lidocaine for NeP.

Miscellaneous agents

Tapentadol is a novel analgesic that has recently become available in Canada. It is pharmacologically similar to tramadol in that it has a dual mechanism of action, but has higher affinity for the mu opioid receptor and has only noradrenergic activity as a monoamine reuptake inhibitor. Tapentadol is approximately one-fifth as potent as oxycodone and has shown efficacy in the management of painful diabetic neuropathy, with greater tolerability (63).

Topical capsaicin may have utility in the management of localized NeP such as postherpetic neuralgia. Following application to the skin, capsaicin initially causes enhanced sensitivity of nociceptors, followed by persistent desensitization after repeated application of low-concentration (<1%) capsaicin or a single application of high-concentration (8%) capsaicin. Several older studies involving small sample sizes indicate that low-concentration capsaicin provides minimal benefit relative to placebo creams (64). On the other hand, high-concentration capsaicin has recently been studied in four trials investigating postherpetic neuralgia and two trials investigating painful HIV neuropathy using 0.04% topical capsaicin as the control to maintain blinding. All of these studies showed significant benefit relative to the control for up to 12 weeks after a single application. The NNT for the postherpetic neuralgia studies was in the range of eight to 10 and, for the HIV-neuropathy studies, was approximately 6.2 (65). High-concentration capsaicin requires preapplication of local anesthetic because of the intense burning sensation it produces. This agent is quite expensive and only available in Canada through compassionate release from Health Canada.

Botulinum toxin has been studied in two RCTs involving NeP. Both studies were positive, with significant reduction in pain intensity for 12 to 14 weeks, but these studies were likely underpowered due to small sample sizes. A crossover trial involving patients with painful diabetic neuropathy included only 18 patients (66) and a parallel design trial involving patients with focal painful neuropathies included only 29 patients (67). Evidence for the role of botulinum toxin in the management of NeP, therefore, remains preliminary.

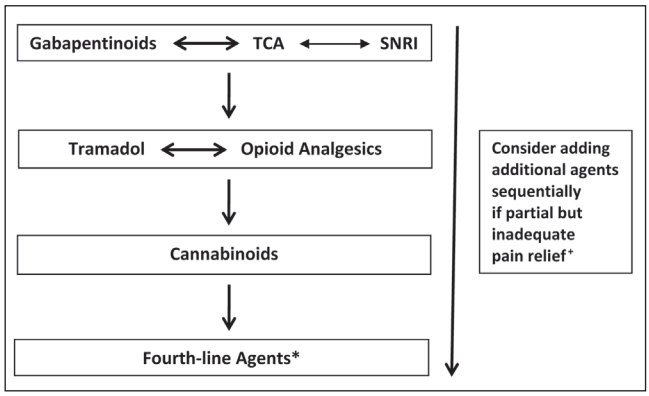

Figure 1) *Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; +Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitors*

Combination pharmacotherapy

Combining ≥2 analgesic agents in the management of NeP is an attractive option because combination pharmacotherapy may improve analgesic efficacy and has the potential to reduce the overall side effect profile if synergistic effects allow for dose reductions of combined drugs (68). A recent Cochrane review of combination pharmacotherapy for the treatment of NeP in adults identified 21 eligible studies (69). The majority of these studies evaluated the combination of an opioid with gabapentin, pregabalin or a TCA, the combination of gabapentin and nortriptyline, and various topical medications. Meta-analysis was possible for only one combination – gabapentin plus opioid versus gabapentin alone. The meta-analysis demonstrated modest superiority of gabapentin plus opioid versus gabapentin alone, although the combination produced significantly more dropouts due to accentuated side effects related to combination treatments. A recent RCT comparing a combination of standard doses of duloxetine (60 mg daily) and pregabalin (300 mg daily) with high-dose monotherapy (duloxetine 120mg daily or pregabalin 600 mg daily) found no significant difference in 24 h average pain, although side effects were comparable (70). Available studies do not support a recommendation of any one specific drug combination for NeP, although these studies do provide a rationale for combination pharmacotherapy.

STEPWISE PHARMACOLOGICAL MANAGEMENT OF NeP

Figure 1 provides an updated algorithm for the pharmacological management of NeP, and Table 1 provides dosing guidelines for selected agents. Nonpharmacological interventions, including physiotherapy, exercise programs and psychological treatment modalities, are essential to enhance outcome.

Relative to the previous guidelines for management of NeP published in 2007 (9), duloxetine has been upgraded from a second-line to a first-line agent based on recent evidence of efficacy in the management of chemotherapy-induced painful neuropathy (35) in addition to previously established efficacy in painful diabetic neuropathy.

TCAs, gabapentinoids and SNRIs are, therefore, now all considered to be first-line agents in the management of chronic NeP. TCAs have the advantage of low cost and once-daily dosing, but can produce drowsiness and significant anticholinergic side effects, including dry mouth, constipation and urinary retention, and are, thus, poorly tolerated in the elderly. Secondary amine TCAs (nortriptyline

TABLE 1
Dosing regimens for selected agents for neuropathic pain

Agent	Starting dose and titration	Usual maintenance dose	Adverse effects	Comments
Tricyclic antidepressants				
Amitriptyline Nortriptyline Desipramine	10–25 mg/day; increase weekly by 10 mg/day	10–100 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significant cardiovascular disease
Serotonin noradrenaline reuptake inhibitors				
Venlafaxine	37.5 mg/day; increase weekly by 37.5 mg/day	150–225 mg/day	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
Duloxetine	30 mg/day; increase weekly by 30 mg/day	60–120 mg/day	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Anticonvulsants				
Gabapentin	100–300 mg/day; increase weekly by 100–300 mg/day	300–1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
Pregabalin	25–150 mg/day; increase weekly by 25–150 mg/day	150–300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
Carbamazepine	100 mg once daily; increase weekly by 100–200 mg/day	200–400 mg three times daily	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for tic douloureux (idiopathic trigeminal neuralgia); as an enzyme inducer, may interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function tests recommended
Controlled-release opioid analgesics				
Morphine	15 mg every 12 h	30–120 mg every 12 h	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for addiction
Oxycodone	10 mg every 12 h	20–60 mg every 12 h		
Fentanyl	12–25 µg/h patch	25–100 µg/h patch		
Hydromorphone	3 mg every 12h	6–24 mg every 12 h		
Others				
Tramadol	50 mg/day; increase weekly by 50 mg/day	50–100 mg four times daily or 100–400 mg daily (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypotension	May lower seizure threshold; use with caution in patients with epilepsy
Lidocaine		5% patches or gel applied to painful areas for 12 h in a 24 h period		Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
Tetrahydro-cannabinol/ cannabidiol (nabiximols)	1–2 sprays every 4 h, maximum 4 sprays on day 1, titrate slowly	Two sprays four times daily	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa)
Nabilone	0.25–0.5 mg at night; increase weekly by 0.5 mg/day	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not test positive for cannabinoids on routine urine drug testing

and desipramine) are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) with comparable analgesic efficacy (71). Cardiac toxicity is also a risk factor with TCAs, which are relatively contraindicated in patients with a history of arrhythmia (72).

Gabapentin and pregabalin appear to be similar in their mechanisms of action and side-effect profiles, and allow for more rapid titration than antidepressant agents. Pregabalin carries the advantage of twice-daily dosing and linear pharmacokinetics relative to gabapentin. Gabapentinoids in general have few drug interactions, but are dependent on renal excretion and, therefore, require dosage reductions in patients with renal insufficiency (72).

If a TCA fails or is contraindicated, the use of a gabapentinoid or an SNRI, such as duloxetine, should be considered. If one of the latter agents provides only partial pain relief, it is reasonable to add the other agent because there is evidence that combination pharmacotherapy can be helpful (68).

When first-line medications fail or provide inadequate pain relief, tramadol or a conventional opioid analgesic may be useful as a second-line treatment. It is also reasonable to consider a short-acting opioid, such as codeine or oxycodone (sometimes combined with acetaminophen), for breakthrough pain during titration of a first-line agent if needed for severe pain. Controlled-release opioid analgesics are considered to be second-line agents in the management of NeP because of their extensive side-effect profile and the risk of opioid misuse, abuse and addiction leading to cautionary prescribing and monitoring. A recent meta-analysis of 62 RCTs found that the most common adverse effects associated with opioids were nausea (28%), constipation (25%), drowsiness (24%), dizziness (18%) and vomiting (15%) (43). Although tolerance may occur to several of these side effects, there is very little tolerance to constipation and almost all patients placed on a controlled-release opioid analgesic require a bowel regimen with continued monitoring of bowel function. Potential long-term complications of opioid

analgesia include opioid-induced hyperalgesia (73) and opioid-induced endocrinopathy (74,75). Endocrine effects manifest as hypogonadism and increased risk for osteopenia. Monitoring for risk for opioid addiction is also challenging. A review suggested that aberrant drug-related behaviours and illicit drug use occurred in 10% to 15% of patients receiving chronic opioid therapy (76). Canadian guidelines for the safe and effective use of opioids for chronic noncancer pain, including monitoring for addiction, are strongly recommended (77).

The cannabinoids have now advanced to third-line agents in the management of chronic NeP based on increasing evidence of efficacy in multiple pain models including HIV neuropathy, post-traumatic and postsurgical NeP, painful diabetic neuropathy and spinal cord injury pain (46,47). However, the cannabinoids also require close monitoring, are contraindicated in patients with a history of psychosis and most of these agents, including the oral mucosal spray, are expensive.

Fourth-line agents in the management of NeP include methadone, tapentadol and anticonvulsants, with lesser evidence of efficacy such as lacosamide, lamotrigine and topiramate. Topical lidocaine has been relegated to fourth-line status because of conflicting evidence of efficacy except in the management of postherpetic neuralgia, for which it remains a second-line option.

It is more challenging to provide a stepwise systematic approach to the management of central NeP because of the relative paucity of high-quality studies and conflicting evidence of efficacy. For instance, lamotrigine was found to be useful in the management of central poststroke pain, but not for spinal cord injury pain (53). Similarly, pregabalin has been found to be efficacious in the management of spinal cord injury pain (29,30), but not in central poststroke pain (33). However, it is reasonable to consider the gabapentinoids and cannabinoids as first-line agents for the management of spinal cord injury pain (78), and TCAs (79) and lamotrigine (53) in the management of central poststroke pain.

INVASIVE TECHNIQUES IN THE MANAGEMENT OF NeP

Although interventional techniques for NeP management are beyond the scope of the present consensus statement, they are usually considered when standard pharmacological treatments fail and psychological screening shows emotional stability. Intravenous lidocaine infusions are generally safe, but evidence of efficacy is limited to one to two weeks postinfusion (80). Two recent comprehensive reviews of interventional management of NeP concluded that weak recommendations could be made for epidural steroid injections for radiculopathy, and spinal cord stimulation for failed back surgery syndrome and complex regional pain syndrome type 1 (81,82).

SUMMARY

The present updated consensus statement provides a stepwise pharmacological approach to the management of NeP. Gabapentinoids, TCAs and SNRIs represent first-line treatments for NeP either individually or in combination. When these agents fail, conventional opioid analgesics and tramadol provide important avenues of treatment, bearing in mind their associated risks and adverse effect profiles. Cannabinoids are now considered to be third-line agents based on recent evidence of efficacy, but also require judicious prescribing practices. Novel treatment approaches are required to improve our management of NeP and further studies are necessary to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes and treatments of pediatric, geriatric and central NeP.

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APPENDIX A: SYSTEMATIC LITERATURE SEARCH RESULTS

Results from Medline and Cochrane databases for pharmacological management of neuropathic pain using TITLE terms 'systematic reviews', 'meta-analyses' and 'guideline OR statement OR recommendation OR consensus' (English language literature since 2007) were tabulated. Articles related to nonpharmacological interventions, cancer pain due to tumour infiltration of nerve, and prevention and epidemiology of neuropathic pain were excluded. A total of 87 systematic reviews and meta-analyses, and 21 consensus statements/guidelines were reviewed. A full list of the included references is available from the authors on request.

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REFERENCES

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630-5.
2. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: A controlled comparison of people with and without diabetes. Diabet Med 2004;21:976-82.
3. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: Proposed classification and research update. Pain 2003;104:1-13.
4. Foley KM. Opioids and chronic neuropathic pain. N Engl J Med 2003;348:1279-81.
5. Gilron I, Watson CP, Cahill CM, et al. Neuropathic pain: A practical guide for the clinician. CMAJ 2006;175:265-75.
6. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380-7.
7. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006;7:281-9.
8. Sadosky A, McDermott AM, Brandenburg NA, Strauss M. A review of the epidemiology of painful diabetic neuropathy, postherpetic neuralgia and less commonly studied neuropathic pain conditions. Pain Pract 2008;8:45-56.
9. Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. BMC Fam Pract 2013;14:28.
10. Kautio AL, Haanpaa M, Kautianen H, Kalso E, Saarto T. Burden of chemotherapy-induced neuropathy – a cross-sectional study. Support Care Cancer 2011;19:1991-1998.
11. Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag 2007;12:13-21.
12. Dworkin RH, Panarites CJ, Armstrong EP, Malone DC, Pham SV. Is treatment of postherpetic neuralgia in the community consistent with evidence-based recommendations? Pain 2012;153:869-75
13. Shekelle P, Eccles MP, Grimshaw JM, Woolf SH. When should clinical guidelines be updated? BMJ 2001;323:155-7.
14. Zakrzewska JM. Medical management of trigeminal neuropathic pains. Expert Opin Pharmacother 2010;11:1239-54.
15. Ashamn EJ, Gronseth GS. Level of evidence reviews – three years of progress. Neurology 2012;79-13-4.
16. Dworkin RH, Turk DC, Basch E, et al. Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy. Pain 2011;152:1705-8.
17. Harden RN, Bruehl SP. Diagnostic criteria: The statistical derivation of the four criterion factors. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: Current Diagnosis and Therapy (Progress in Pain Research and Management, Volume 32). Seattle: IASP Press, 2005:45-58.
18. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.
19. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinic and postal research. J Pain 2005;6:149-58.
20. Cohen J. Statistical Power Analysis for the Behavioural Sciences. New York, San Francisco, London: Academic Press, 1988.
21. Taylor CP. The biology and pharmacology of calcium channel alpha2-delta proteins. CNS Drug Rev 2004;10:183-8.
22. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113-23.
23. Gordh TE, Stubhaug A, Jensen TS, et al. Gabapentin in traumatic nerve injury pain: A randomized, double-blind, placebo-controlled, crossover, multi-centre study. Pain 2008;138:255-66.
24. Rao RD, Michalak JC, Sloan JA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 2007;110:2110-8.
25. Rintala DH, Holmes SA, Courtade D, et al. Comparison of the effectiveness of amitriptryline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Arch Phys Med Rehabil 2007;88:1547-60.
26. Smith DG, Ehde DM, Hanley MA, et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. J Rehabil Res Dev 2005;42:645-54.
27. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathy pain. Pain 2010;150:573-81.
28. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Neurology 2011:1-8.
29. Siddall PJ, Cousins MJ, Otte A, et al. Pregabalin in central neuropathic pain associated with spinal cord injury: A placebo-controlled trial. Neurology 2006;67:1792-800.
30. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain 2008;136:150-7.
31. Baron R, Freynhagen R, Tolle TR, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain 2010;150:420-7.
32. Philip R, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: A randomized withdrawal trial. Clin J Pain 2014;30:379-90.
33. Kim JS, Bashford G, Murphy TK, et al. Safety and efficacy of pregabalin in patients with central post-stroke pain. Pain 2011;152:1018-23.
34. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: An evidence-based proposal. Pain 2005;118:289-305.
35. Lavoie Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. JAMA 2013;309:1359-67.
36. Vranken JH, Hollmann MW, van der Vegt MH, et al. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: A randomized, double-blind, placebo-controlled trial. Pain 2011;152:267-73.

37. Rowbotham MC, Goli V, Junz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: A double-blind, placebo-controlled study. Pain 2004;100:697-706. (Erratum in 2005;113:248).
38. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: A randomized, controlled trial. Neurology 2003;60:1284-9.
39. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. J Clin Neuromuscul Dis 2001;3:53-62.
40. Abramowicz M. Tramadol – a new oral analgesic. Med Lett Drugs Ther 1993;37:59-62.
41. Smith AB, Ravikumar TS, Kamin M, et al. Combination tramadol plus acetaminophen for postsurgical pain. Am J Surg 2004;187:521-7.
42. Hollingshead J, Duhmke RM, Cornblath DR. Tramadol for neuropathic pain. Cochrane Database Syst Rev 2006;(3):CD003726.
43. Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag 2011;16:337-51.
44. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized double-blind placebo-controlled crossover trial. BMJ 2004;329:253.
45. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-9.
46. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: A systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735044.
47. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain 2012;153:2073-82.
48. Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther 1992;52:547-52.
49. Sindrup SH, Cram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990;42:135-44.
50. Otto M, Bach FW, Jensen TS, Brosen K, Sindrup SH. Escitalopram in painful polyneuropathy: A randomized, placebo-controlled, crossover trial Pain 2008;139:275-83.
51. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250-6.
52. Sproule BA, Naranjo CA, Brenmer KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions. A critical review of the evidence. Clin Pharmacokinet 1997;33:454-71.
53. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. Cochrane Database Syst Rev 2011;(2):CD006044.
54. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012;(2):CD009318.
55. Gorman A, Elliott K, Inturrisi C. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett 1997;223:5-8.
56. Morley JD, Bridson J, Nash TP, et al. Low dose methadone has an analgesic effect in neuropathic pain: A double-blind randomized controlled crossover trial. Palliat Med 2003;17:576-87.
57. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. Pain Res Manag 2003;8:149-54.
58. Moulin DE, Palma D, Watling C, Schulz V. Methadone in the management of intractable neuropathic noncancer pain. Can J Neurol Sci 2005;32:340-3.
59. Lynch M. A review of the use of methadone for the treatment of chronic noncancer pain. Pain Res Manag 2005;10:133-44.
60. Gammaaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. Ann Pharmacother 2002;36:236-40.
61. Cheville AL, Sloan JA, Northfelt DW, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: A phase III double-blind crossover study (N01CB). Support Care Cancer 2009;17:451-60.
62. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clin J Pain 2008;24:51-5.
63. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: Results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27:151-62.
64. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2012;(9):CD010111.
65. Derry S, Rice, AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2013;(2):CD007393.
66. Yuan R-Y, Sheu J-J, Yu J-M, et al. Botulinum toxin for diabetic neuropathic pain. Neurology 2009;72:1473-8.
67. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. Ann Neurology 2008;64:274-83.
68. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: From bench to bedside. Lancet Neurol 2013;12:1084-95.
69. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev 2012(7):CD008943.
70. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 2013;154:2616-25.
71. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996;68:217-27.
72. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: An overview of recent guidelines. Amer J Med 2009;122(10A):S22-S32.
73. Mao J. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. Pain 2002:100:213-7.
74. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain 2002;3:377-84.
75. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain 2008;9:28-36.
76. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviours? A structured evidence-based review. Pain Med 2008;9:444-59.
77. National Opioid Use Guideline Group (NOUGG). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. <http://nationalpaincentre mcmaster ca/opioid/.2010> (Accessed September 2013).
78. Teasell RW, Mehta W, Aubut JL, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil 2010;91:816-31.
79. Leijon G. Boivie J. Central post-stroke pain – a controlled trial of amitriptyline and carbamazepine. Pain 1989;36:27-36.
80. Tremont-Lukats IW, Challapalli V, McNicol ED, et al. Systemic administration of local anesthetics to relieve neuropathic pain: A systematic review and meta-analysis. Anesth Analg 2005;101:1738-49.
81. Mailis A, Taenzer P. Evidence-based guideline for neuropathic pain interventional treatments: Spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. Pain Res Manag 2012;17:150-8.
82. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;54:2249-61.

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ORIGINAL ARTICLE

A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

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Sativex, a THC/CBD fixed dose combination oromucosal spray, does not have an INN. Nabiximols is the FDA US Adopted Name (USAN)

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Conflicts of interest
M. Serpell, S. Ratcliffe, J. Hovorka, M. Schofield and E. Ehler were all investigators in this study and received investigator fees from GW accordingly for their participation in the study. GW medical writers L. Taylor and H. Lauder undertook the initial compilation and quality control review of the manuscript. Together with the other authors, the target journal was then agreed and all authors reviewed and contributed to the content of the manuscript, and agreed upon the final submitted version. All Intellectual Property Rights arising out of the current clinical study are vest in or exclusively licensed to GW.

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Abstract

Background: Peripheral neuropathic pain (PNP) associated with allodynia poses a significant clinical challenge. The efficacy of Δ^9-tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray, a novel cannabinoid formulation, was investigated in this 15-week randomized, double-blind, placebo-controlled parallel group study.

Methods: In total, 303 patients with PNP associated with allodynia were screened; 128 were randomized to THC/CBD spray and 118 to placebo, in addition to their current analgesic therapy. The co-primary efficacy endpoints were the 30% responder rate in PNP 0–10 numerical rating scale (NRS) score and the mean change from baseline to the end of treatment in this score. Various key secondary measures of pain and functioning were also investigated.

Results: At the 30% responder level, there were statistically significant treatment differences in favour of THC/CBD spray in the full analysis (intention-to-treat) dataset [$p = 0.034$; 95% confidence interval (CI): 1.05–3.70]. There was also a reduction in mean PNP 0–10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance. Secondary measures of sleep quality 0–10 NRS score ($p = 0.0072$) and Subject Global Impression of Change (SGIC) ($p = 0.023$) also demonstrated statistically significant treatment differences in favour of THC/CBD spray treatment.

Conclusions: These findings demonstrate that, in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in pain, sleep quality and SGIC of the severity of their condition are obtained with THC/CBD spray. THC/CBD spray was well tolerated and no new safety concerns were identified.

What's already known about this topic?

- Neuropathic pain is a debilitating form of chronic pain and can be difficult to treat, with only approximately half of sufferers achieving partial relief, often requiring the use of novel analgesics due to the ineffectiveness of conventional pharmacotherapies.
- Cannabinoids, including Δ^9-tetrahydrocannabinol/cannabidiol (THC/CBD) spray, have demonstrated efficacy in addressing this unmet need. A previous randomized controlled trial in neuropathic pain patients demonstrated positive effects in pain and allodynia at 5 weeks.

What does this study add?

- The study demonstrates that THC/CBD spray can provide clinically relevant improvements in pain, sleep quality and patient global impression of the change in their condition in a meaningful proportion of usually treatment-resistant patients.
- This supports the hypothesis that THC/CBD could be a useful candidate for peripheral neuropathic pain treatment, demonstrating efficacy in a few key outcomes over a much longer period of time (15 weeks compared to 5 weeks).

1. Introduction

Neuropathic pain is a chronic, debilitating and widespread condition with an estimated prevalence of over 1% (Backonja and Serra, 2004). Two recent population-based studies in Europe estimated the prevalence of chronic neuropathic pain, or pain with neuropathic characteristics, to be 8% and 7%, respectively (Torrance et al., 2006; Bouhassira et al., 2008). Neuropathic pain can be triggered by a variety of diseases and conditions, but the mechanisms that establish and maintain it are specific to the characteristics of the damage and/or dysfunction of the nervous system. Allodynic pain, characterized as pain evoked by a normally non-nociceptive stimulus (such as temperature), is a subgroup of peripheral neuropathic pain (PNP) and can be very difficult to treat.

A mechanistic approach to neuropathic pain is currently believed to represent the optimal means of symptom management (Jensen et al., 2001; Woolf and Max, 2001). However, there is little clinical proof that this approach is the most effective strategy. Existing therapies for PNP include tricyclic and related antidepressants, anti-epileptic agents and opioids (Attal et al., 2006). However, these therapies may have only a limited effect on PNP, and the side-effect problems associated with each are well known.

The endocannabinoid system modulator, Δ^9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray, is formulated from plant-based extracts prepared from genetically distinct chemotypes of *Cannabis sativa* L. and contains an approximately 1:1 ratio of THC : CBD, plus smaller amounts of other compounds, including minor cannabinoids and terpenes (Russo, 2011). It was recently licensed for use in various European countries for the relief of spasticity in multiple sclerosis (MS) (MHRA Public Assessment Report, 2010), as well as outside the European Union (in Canada, Israel, New Zealand). THC/CBD spray is also licensed for use in Canada for the treatment of central neuropathic pain (CNP) in MS patients.

Cannabinoids are thought to act primarily via specific receptors, designated cannabinoid receptor-1 (CB_1) and cannabinoid receptor-2 (CB_2). CB_1 receptors are predominantly distributed throughout the nervous systems, while CB_2 receptors are primarily located in the periphery, especially the immune system (Howlett et al., 2002).

Cannabinoids are postulated to offer a new therapeutic approach to neuropathic pain treatment. Previous studies using synthetic THC and a synthetic metabolite of THC demonstrated effects in patients on CNP (Svendsen et al., 2004) and PNP associated with allodynia (Karst et al., 2003), respectively. Furthermore, in a previous randomized controlled trial (RCT) (Rog et al., 2005) and in an open-label extension study (Rog et al., 2007), GW has shown that THC/CBD spray has pain relieving effects in neuropathic pain associated with MS and in difficult to treat pain following brachial plexus avulsion (Berman et al., 2004). In addition, a previous 5-week GW study of THC/CBD spray in the treatment of PNP concluded that THC/CBD spray is an effective treatment, which provided a rapid clinically relevant improvement (Nurmikko et al., 2007).

The objectives of this study were to investigate the therapeutic benefits of 15-week THC/CBD spray treatment on PNP associated with allodynia, as well as associated sleep disturbance and patient quality of life.

2. Methods

2.1 Study design

This was a 15-week (1-week baseline and 14-week treatment period), multi-centre, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy of THC/CBD spray in patients with PNP associated with

allodynia. The study took place at 21 centres in the United Kingdom (UK), seven centres in Czech Republic, six centres in Romania, four centres in Belgium and one centre in Canada. The study was approved by the relevant Institution Review Board or Ethical Committee in each country and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent to take part in the study.

All visits took place at study centres. Following eligibility screening, patients completed a 7-day baseline period. Patients were then assessed, randomized and received dose introduction. Visits occurred at the end of weeks 2, 6, 10 and at the end of the study (treatment week 14) or earlier if they withdrew. A follow-up visit occurred 28 days after study completion or withdrawal. Patients were then given the opportunity to enrol in an open-label extension study. Results from the open-label extension study will not be presented in this report.

At each visit, the following information was recorded: adverse events (AEs), vital signs, intoxication 0–10 numerical rating scale (NRS), sleep quality 0–10 NRS, PNP 0–10 NRS, neuropathic pain scale (NPS), use of rescue analgesia, any changes in current medical conditions, dose of regular maintenance analgesic, changes in concomitant medication, current dose of study medication and medication compliance. Clinical laboratory sampling (haematology, biochemistry and urinalysis) was carried out at screening and at the end of treatment.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

Eligible patients were aged 18 or older, had mechanical allodynia within the territory of the affected nerve(s) (confirmed by either a positive response to stroking the allodynic area with a SENSELAB™ Brush 05 (Somedic AB, Hörby, Sweden) or to force applied by a 5.07 g Semmes-Weinstein monofilament), at least a 6-month history of PNP, and were receiving the appropriate treatment for their PNP. Eligible patients had at least one of the following underlying conditions, which caused their PNP: post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or Complex Regional Pain Syndrome (CRPS) type 2. Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) during the baseline period (average 0–10 NRS score of 4/10), and pain that was not wholly relieved by their current therapy. In addition, their analgesic regimen was stable for at least 2 weeks preceding study entry and they were willing for the responsible authorities (i.e., primary care consultant or physician) to be notified of their participation in the study.

2.2.2 Exclusion criteria

Patients with severe pain from other concomitant conditions were excluded, as were those with a history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders, or with a known hypersensitivity to the study medication. Those with CRPS type 1, cancer-related PNP or pain resulting from diabetes mellitus were excluded. Patients receiving a prohibited medication [including cannabis or cannabinoid-based medications (in the last year), any analgesics taken on a 'PRN' (when required) basis, the introduction of any new analgesic medication, or any alteration to the dosage of the patient's concomitant analgesic medication (other than the rescue analgesia provided), or all paracetamol-containing medications (stopped on the day the patient entered the baseline period)], who were unwilling to abstain for the study duration were also excluded, as were those with a known history of alcohol or substance abuse. Women of child-bearing potential or their partners were excluded unless willing to ensure effective contraception was used throughout the study, as were those who had received an investigational medicinal product within 12 weeks of screening. Pregnant or lactating women and those planning a pregnancy were excluded. Patients with any physical abnormality at screening (i.e., any abnormalities that, in the opinion of the investigator, would prevent the patient from safely participating in the study), or those intending to travel or donate blood during the study were also ineligible to take part.

2.3 Study medication and procedures

A pump action oromucosal spray was used to deliver study medication. Each 100 μL spray of THC/CBD delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa, and each spray of placebo delivered the excipients plus colorants. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. Patients self-administered the medication to their optimal dose, but were restricted to a maximum of eight sprays in a 3-h period up to a maximum of 24 sprays per 24-h period. Initially, patients began at a maximum of one spray per 4-h period. Thereafter patients were advised to self-titrate their medication to symptom relief or maximum dose, but increases were limited to a maximum of 50% of the previous day's dose.

2.3.1 Concomitant medications

As would be expected in this group of patients, many were receiving concomitant medications for analgesia and were allowed to continue their concomitant analgesic medication, with the exception of paracetamol (acetaminophen), provided that a stable dose was maintained throughout the study. Patients were not permitted to take analgesics on a 'PRN' (when required) basis, and the introduction of any new analgesic medication or any alteration to the dosage of the patients' concomitant analgesic medication (other than the rescue analgesia provided) was prohibited during the study. The rescue analgesia provided contained paracetamol Ph Eur 500 mg. The maximum single dose was two 500 mg tablets, and the maximum total daily dose was 4 g (i.e., 8

tablets per day). A single dose was not to be taken more frequently than every 4 h, with no more than four doses in any 24-h period.

2.4 Study endpoints

2.4.1 Primary efficacy endpoints

In this study, a 0–10 NRS was used as the primary measure of pain severity. The efficacy endpoints for analysis were the proportion of patients showing a 30% or more improvement from baseline to the end of treatment in PNP 0–10 NRS score, and the mean change in PNP 0–10 NRS score from baseline to the end of treatment. End of treatment PNP 0–10 NRS scores were the average of all scores during the last 7 days of the evaluable treatment period.

The PNP 0–10 NRS was recorded daily by patients in their diary books. Each patient was instructed to complete their PNP 0–10 NRS score by reviewing their day's pain at the end of every day. Patients were asked, 'On a scale of "0 to 10", please indicate the average level of your nerve pain over the last 24 h', with the anchors: 0 = 'no pain', 10 = 'worst possible pain'. The assessment reviewed the entire day's pain, and therefore, the perception of pain was less likely to be influenced directly by sleep, compared with an assessment made on waking. Patients were instructed to relate 'no pain' to the time prior to their onset of their PNP associated with allodynia.

2.4.2 Secondary efficacy endpoints

Secondary endpoints included the mean changes from baseline to the end of treatment in the following scores: NPS, sleep quality 0–10 NRS, Subject Global Impression of Change (SGIC), Brief Pain Inventory (short form) (BPI-SF), dynamic and punctate allodynia tests, quality of life (EQ-5D) health questionnaire, as well as the proportion of patients showing a 50% or more improvement in PNP 0–10 NRS score, and the use of rescue analgesia.

2.4.2.1 NPS

The NPS (neuropathic pain scale PDF) was collected weekly in the patient diaries during the whole length of the study. The variable for analysis was the change in mean NPS score from baseline (mean of two assessments during the baseline period) to the end of the study (mean of last two assessments during the evaluable period).

The NPS consists of 10 individual items. Nine of these provide a total of ten 0–10 NRS responses and there is a multi-part free text question. The NPS score to be used for the analysis was the sum of the ten 0–10 NRS responses. If up to three individual items were missing, then an NPS score was imputed by multiplying the mean of the completed items by 10. If more than three individual items were missing, then the whole score was missing.

2.4.2.2 Sleep quality 0–10 NRS

Sleep quality was assessed at all study visits on a 0–10 NRS, with the main variable for analysis being the change from baseline to the end of treatment in sleep quality 0–10 NRS score. The sleep quality 0–10 NRS was completed at the same time each day, i.e., bedtime in the evening. The patient was asked 'on a scale of "0 to 10", please indicate how your pain disrupted your sleep last night', with the anchors: 0 = 'did not disrupt sleep' and 10 = 'completely disrupted (unable to sleep at all)'.

2.4.2.3 SGIC

At baseline, patients wrote a brief description of their pain caused by peripheral neuropathy, which was used at the end of treatment to aid their memory regarding their symptoms at the start of the study. The SGIC was completed at the end of treatment. A 7-point Likert-type scale was used to evaluate the patients' perception of their condition, and patients were asked, 'Please assess the status of your pain due to peripheral neuropathy since entry into the study using the scale below', with the anchors: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse' or 'very much worse'.

2.4.2.4 BPI-SF

The BPI-SF (Cleeland and Ryan, 1994) was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. The BPI-SF consists of nine questions, each of which consists of a single response apart from question 9, which is sub-divided into seven parts (9A–9G). Questions 3–6 ask patients to rate pain on a 0–10 scale over the prior week (where 0 = 'no pain' and 10 = 'pain as bad as you can imagine'). Severity is measured as worst pain, least pain, average pain and pain right now. The severity composite score was calculated as the arithmetic mean of the four severity items (range 0–10). The minimum value is zero and maximum is 10.

The BPI-SF also records the degree to which pain interferes with activities on a 0–10 scale (where 0 = 'does not interfere at all' and 10 = 'pain completely interferes with activity'). As such, a higher score represents a poorer outcome.

Two composite scores were calculated from the BPI-SF:
(1) The pain severity composite score: the arithmetic mean of the four pain scores (questions 3–6) and represents the pain intensity.
(2) The pain interference composite score: the arithmetic mean of the seven interference items (questions 9A–9G) and represents the effect of pain.

2.4.2.5 Dynamic allodynia test

The dynamic allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analy-

sis. At each time point, dynamic allodynia was assessed by stroking the skin over the affected area five times with a SENSELAB Brush 05, designed specifically for sensory testing at 5-s intervals, and recording the pain severity on a 0–10 NRS, where 0 = 'no pain' and 10 = 'most pain imaginable'. All strokes were of the same length, minimum 2 cm. The mean of the five scores for the identified allodynic area only was calculated to define the dynamic allodynia pain score.

2.4.2.6 Punctate allodynia test

The punctate allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure was applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). Patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 = 'no pain' and 10 = 'most intense pain imaginable'. The average of the ascending pain threshold forces, as available, for the identified allodynic area only was calculated to define the punctate allodynia pain threshold force.

2.4.2.7 EQ-5D questionnaire

The EQ-5D questionnaire (The Euroqol Group, 1990) was completed twice during the study, once at baseline and once at the end of treatment.

The EQ-5D questionnaire provided two outcomes:

(1) A weighted health state index visual analogue scale (VAS).

(2) A self-rated health status VAS.

The self-rated health status VAS anchors were: 0 = 'worst health state imaginable' to 100 = 'best health state imaginable'. The weighted health state index used the same VAS as above but was calculated for each assessment without imputation to account for missing values, i.e., if one or more individual items were missing, then the whole index was missing.

The change from baseline to the end of treatment was calculated for both VASs.

2.4.2.8 Use of rescue analgesia

Use of breakthrough medication was recorded daily during the study as the number of paracetamol tablets taken. The change in mean daily quantities of tablets used was calculated from baseline to the last 7 days of treatment.

2.4.3 Safety endpoints

The safety endpoints were the incidence of AEs and serious adverse events (SAEs), clinical laboratory sampling pre- and post-treatment, vital signs, oral examination and intoxication 0–10 NRS.

2.4.4 Sample size

Based upon previous GW studies, it was believed that this study would result in a difference in the primary endpoint between THC/CBD spray and placebo patients of at least 0.9 points on the PNP 0–10 NRS. Also based on previous GW studies and the literature, it was estimated that the standard deviation of the changes from baseline in the primary endpoint would be approximately 2.1 points (Rowbotham et al., 1998; Rice et al., 2001; Serpell and Neuropathic Pain Study Group, 2002; Boureau et al., 2003). Taking this into account, for a significance level of 5% and 80% power, we would need a total of 174 evaluable patients (87 in each group) to detect a difference of 0.9 points in the PNP 0–10 NRS. Allowing for 20% of randomized patients to be unevaluable, then 218 patients (109 in each group) would need to be randomized.

2.5 Method of assigning patients to treatment groups and blinding

Patients were randomized to receive either THC/CBD spray or placebo. Randomization was carried out using a predetermined computer-generated randomization code, produced by the GW Biometrics Department, in which treatment allocation was made using permuted blocks of four. Study medication was pre-packed by the GW Clinical Trial Supplies Department and dispatched to the investigator centres labelled with patient numbers. The randomization scheme involved patient numbers being assigned sequentially by the investigator staff.

Study medication was provided in 5.5-mL type I amber glass vials labelled with the GW name, study code, patient number, visit number and the expiry date. The investigator staff, pharmacy and GW Clinical Department held sealed code break envelopes for each patient. Since THC/CBD spray is a plant-based extract in alcoholic solution with a distinctive smell, taste and colour, both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. The placebo also contained quinoline and sunset yellow, to match the colour of the plant extract. As such, participants, investigators are caregivers were all blinded to the treatment allocation.

2.6 Statistical methods

All randomized patients who received at least one dose of test treatment and had on-treatment efficacy data were included in the intention-to-treat (ITT) analysis set. The per protocol (PP) analysis set included those with evaluable data for the primary parameter with no protocol deviations, which were considered to affect the comparison between treatments for this endpoint. All summaries and statistical analyses were performed using SAS Version 9.1 (SAS Insti-

tute Inc., Cary, NC, USA). Statistical comparisons of efficacy data between treatments used two-sided statistical tests at the 5% significance level. PNP 0–10 NRS scores were evaluated by analysis of covariance (ANCOVA), with baseline values as covariate and treatment group and centre group as main effect. These tests were performed at the 10% significance level as a possible indicator of an interactive effect. An additional analysis was performed on the PNP 0–10 NRS dataset to assess the time course of the treatment effect using repeated measures. A multivariate linear model was used with a separate unstructured covariance matrix in each treatment arm. The mean (fixed effects structure) incorporated full treatment-by-(categorical) time interaction. Baseline was included as a covariate, together with baseline-by-time interaction. Grouped centre was included as a categorical covariate. The fitted model was also used to produce a final time point comparison.

Changes from baseline to the end of treatment were compared between treatment groups using ANCOVA for the following secondary endpoints: NPS, dynamic allodynia pain score, punctate allodynia pain score, BPI-SF, sleep quality 0–10 NRS and EQ-5D. Models included treatment and centre group as factors and baseline mean usage as a covariate.

The change from baseline in mean daily quantity of rescue analgesia usage was analysed in a fashion similar to the PNP 0–10 NRS.

In the SGIC outcome, the two treatment groups were compared using ordinal logistic regression and the proportional odds model, incorporating centre group.

2.7 Amendments during trial

The following inclusion criterion was removed: 'Subject has at least moderate PNP, which is defined as the total of the two NPS scores before randomization being at least 80'. After ethics approval had been granted for the study, the Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment of Neuropathic Pain were finalized and issued (CPMP guideline, 2004). The CHMP guidance notes clearly recommended that the 0–10 NRS should be used as the primary efficacy endpoint. Therefore, to have an entry criterion of the two NPS scores before randomization being at least 80 in addition to the minimum 0–10 NRS pain scores was considered futile. The NPS was still collected as a secondary outcome measure and analysed and reported accordingly.

3. Results

The study took place between 27 September 2005 and 18 October 2006. In total, 303 patients were recruited and 246 were randomized and analysed at 39 study centres. Of these, 128 received THC/CBD spray, 118 received placebo and 57 were withdrawn before randomization. A total of 173 patients completed the study, 21 ceased treatment but remained in the study, and 52 withdrew. Six patients (one taking placebo and five taking THC/CBD spray) were not included in the analysis as they had no on-treatment efficacy data. A summary of the flow of the trial can be found in Fig. 1. The mean duration of the underlying neuropathic condition in these patients was similar between treatment groups at approximately 6 years with the minima and maxima also being similar at 0.6–38.1 years for THC/CBD spray and 0.4–39.3 years for placebo groups, respectively. The duration of their treatment-resistant neuropathic pain was also similar and no notable differences in the proportions of patients with each type of underlying condition were seen between treatment groups, the most common of which was focal nerve lesions for both groups. These and other study population demographics are displayed in Table 1. Overall, the mean daily dose of THC/CBD spray was 8.9 sprays and for placebo was 14.2 sprays, and the median duration of treatment was 78.2 days for THC/CBD spray and 86.4 days for placebo.

3.1 Concomitant medication

The majority of patients (90% overall) continued to take analgesics during the study. The most commonly reported classes of analgesic were non-selective monoamine reuptake inhibitors (tricyclic antidepressants) taken by 26% of patients, anti-epileptics (pregabalin) taken by 20% of patients and other anti-epileptics (gabapentin) taken by 23% of patients. In addition, 19% and 18% of patients, respectively, took natural opium alkaloids (such as dihydrocodeine) and other opioids (mostly tramadol). The most commonly reported classes of non-analgesic concomitant medication were proton pump inhibitors (18%), HMG Co-A reductase inhibitors (statins, 15%), angiotensin-converting enzyme inhibitors (14%) and beta blocking agents (13%).

3.2 Primary endpoint: 30% responder analysis and change from baseline to the end of treatment in PNP 0–10 NRS

A total of 34 patients (28%) receiving THC/CBD spray were classified as responders at the 30% level compared with 19 patients (16%) on placebo. Responder analysis at this level showed a statistically significant treatment difference in the evaluable period for the ITT population with an odds ratio of 1.97 ($p = 0.034$; 95% CI: 1.05–3.70), in favour of THC/CBD spray treatment (Table 2). This finding was supported by the PP analysis set, in which 27 (36%) of patients in the THC/CBD spray treatment group achieved at least a

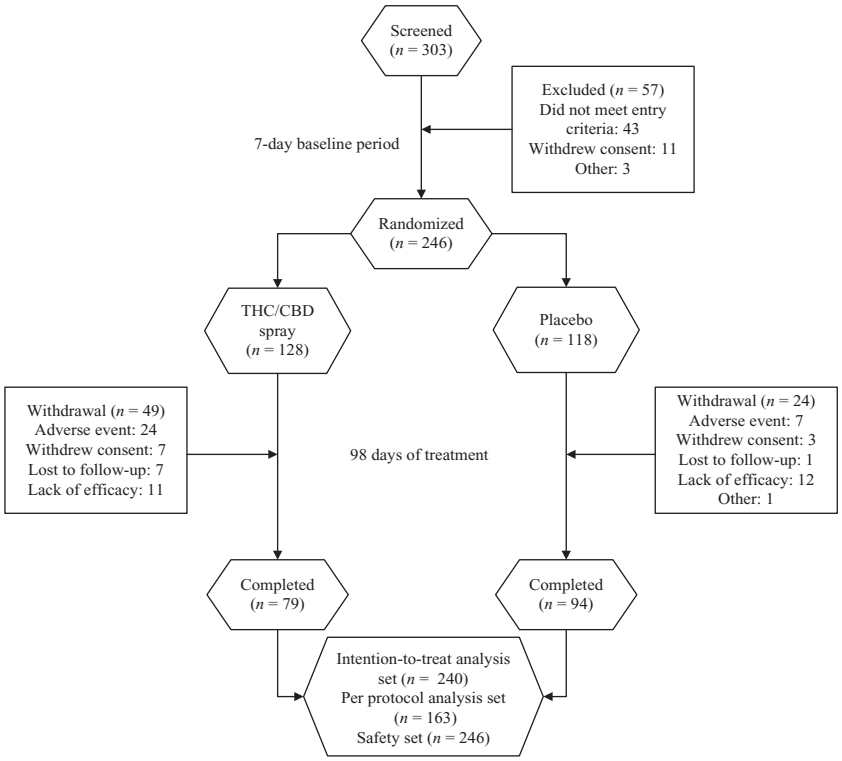

Figure 1 Breakdown of patients enrolled in the study.

30% improvement in 0–10 NRS pain scores compared with 18 (20%) in the placebo treatment group, with an odds ratio of 2.27 ($p = 0.021$; 95% CI: 1.12–4.57) (Table 2). For 30% responders, the proportion of responders was observed to increase much more quickly in relation to the dose of THC/CBD spray compared with placebo, as illustrated in Fig. 2. At a point of around 14–15 sprays per day, the response rate in

Table 1 Demographics and baseline characteristics for all patients who took part in the study.

	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)	Total (*n* = 246)
	No. of patients (%)		
Gender			
Male	43 (34)	53 (45)	96 (39)
Female	85 (66)	65 (55)	150 (61)
Ethnic origin			
White/Caucasian	127 (99)	116 (98)	243 (99)
Black/African American	0	2 (2)	2 (1)
Other	1 (1)	0	1 (< 0.5)
Previous cannabis use in the last year	13 (10)	12 (10)	25 (10)
Type of underlying condition causing neuropathic pain			
Post-herpetic neuralgia	34 (27)	30 (25)	64 (26)
Peripheral neuropathy	35 (27)	25 (21)	60 (24)
Focal nerve lesion	44 (34)	52 (44)	96 (39)
Complex regional pain syndrome-II	17 (13)	14 (12)	31 (13)
	Mean (SD)		
Age (years)	57.6 (14.4)	57.0 (14.1)	57.3 (14.2)
Body mass index (kg/m^2)	28.4 (6.5)	27.3 (4. 9)	27.9 (5.8)
Duration of neuropathic condition (years)	6.3 (6.7)	6.3 (6.4)	6.3 (6.6)
Duration of peripheral neuropathic condition (years)	5.7 (6.3)	5.2 (5.4)	5.5 (5.9)

CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

Table 2 Summary of the analysis of all primary and secondary efficacy endpoints (ITT and PP analysis sets). Treatment differences between THC/CBD spray and placebo are presented using change from baseline to the end of treatment data for each endpoint, unless otherwise stated.

Endpoint	ITT analysis set			PP analysis set		
Primary endpoints						
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
30% responder analysis (PNP 0–10 NRS)	1.970	1.049 to 3.702	0.034	2.266	1.124 to 4.568	0.021
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
PNP 0–10 NRS	–0.34 (0.230)	–0.79 to 0.11	0.139	–0.48 (0.303)	–1.08 to 0.12	0.116
Secondary endpoints						
	Treatment difference (SE)	95% CI	*p*-value	Treatment difference (SE)	95% CI	*p*-value
NPS	–2.86 (2.211)	–7.22 to 1.50	0.198	–5.26 (2.873)	–10.94 to 0.41	0.069
Sleep quality 0–10 NRS	–0.83 (0.306)	–1.43 to –0.23	0.007	–0.91 (0.369)	–1.63 to –0.18	0.015
BPI-SF (pain severity composite score)	–0.25 (0.236)	–0.72 to 0.21	0.288	–0.27 (0.291)	–0.85 to 0.30	0.349
BPI-SF (average pain)	–0.34 (0.237)	–0.81 to 0.12	0.148	–0.47 (0.299)	–1.06 to 0.13	0.122
BPI-SF (worst pain)	–0.30 (0.265)	–0.82 to 0.22	0.255	–0.39 (0.322)	–1.02 to 0.25	0.234
BPI-SF (pain interference composite score)	–0.32 (0.241)	–0.80 to 0.15	0.183	–0.39 (0.304)	–0.99 to 0.21	0.204
Dynamic allodynia test	0.08 (0.305)	–0.52 to 0.68	0.795	–0.27 (0.359)	–0.98 to 0.44	0.460
Punctate allodynia test	–0.14 (0.118)	–0.37 to 0.09	0.233	–0.06 (0.150)	–0.35 to 0.24	0.701
EQ-5D (weighted health status index VAS)	–0.01 (0.024)	–0.06 to 0.04	0.617	–	–	–
EQ-5D (self-rated health status VAS)	–0.75 (2.459)	–5.60 to 4.09	0.760	–	–	–
Use of rescue analgesia	–0.38 (0.237)	–0.85 to 0.09	0.112	0.40 (0.316)	–1.02 to 0.23	0.211
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
50% responder analysis (PNP 0–10 NRS)	1.699	0.645 to 4.476	0.280	2.045	0.750 to 5.576	0.157
SGIC (end of treatment only)	1.762	1.080 to 2.876	0.023	2.988	1.661 to 5.378	0.0003

BPI-SF, Brief Pain Inventory (short form); CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; PP, per protocol; SGIC, Subject Global Impression of Change; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

patients receiving THC/CBD spray slowed, while for those taking placebo, the proportion of responders was still increasing maximally.

In the co-primary endpoint of change from baseline to the end of treatment in PNP 0–10 NRS score, for the ITT and PP datasets, the adjusted mean reduction in PNP 0–10 NRS score gave respective estimated treatment differences of –0.34 points ($p = 0.14$; 95% CI: –0.79 to 0.11 points) and –0.48 points ($p = 0.12$; 95% CI: –1.08 to 0.12 points), in favour of a benefit with

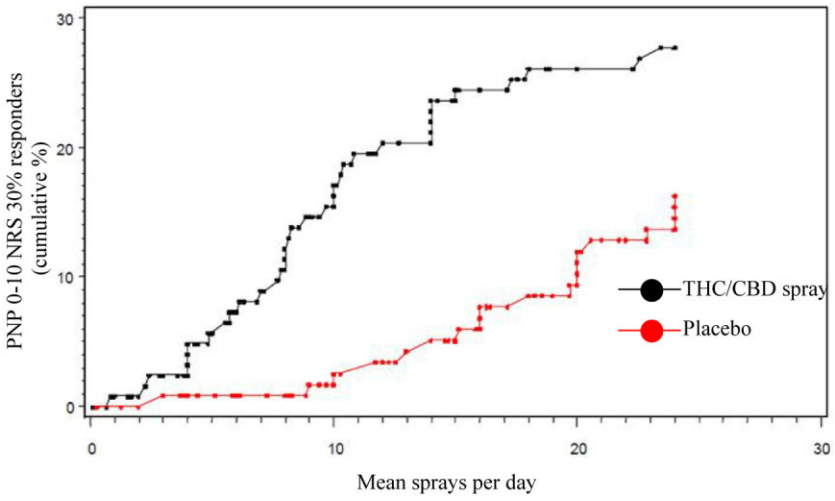

Figure 2 Cumulative percentage of responders at the 30% level by mean sprays.

Table 3 Sleep quality ratings by study visit, ITT and PP datasets.

	Adjusted mean change from baseline			
	THC/CBD spray (n = 122)	Placebo (n = 117)	Treatment difference (THC/CBD spray vs. placebo)	Lower and upper limits 95% CI
Time point	ITT			
Visit 3 (day 15)	−1.44	−0.73	−0.70	−1.22, −0.19
Visit 4 (day 43)	−1.45	−0.74	−0.71	−1.31, −0.11
Visit 5 (day 71)	−1.39	−0.66	−0.74	−1.34, −0.13
Visit 6 (day 99)	−1.47	−0.69	−0.78	−1.36, −0.21
Final visit (day 127)	−1.57	−0.74	−0.83	−1.43, −0.23
	PP			
	(n = 73)	(n = 89)		
Visit 3 (day 15)	−1.46	−0.81	−0.65	−1.30, −0.01
Visit 4 (day 43)	−1.62	−0.83	−0.78	−1.58, 0.01
Visit 5 (day 71)	−1.52	−0.71	−0.81	−1.58, −0.03
Visit 6 (day 99)	−1.49	−0.58	−0.91	−1.63, −0.18
Final visit (day 127)	−1.49	−0.58	−0.91	−1.63, −0.18

CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; PP, per protocol; THC, Δ^9-tetrahydrocannabinol.

THC/CBD spray treatment. However, these failed to reach statistical significance.

3.3 Secondary efficacy analysis

At the 50% responder level in the PNP 0–10 NRS score analysis, the treatment difference was also in favour of the THC/CBD spray treatment group in both the ITT and the PP populations, but did not reach statistical significance in either population (Table 2).

For the ITT complete period, the adjusted mean sleep quality 0–10 NRS score decreased (improved) by 1.57 points from a mean baseline score of 5.4 points in the THC/CBD spray group, compared with an adjusted decrease of 0.74 points from a baseline of 5.8 points in the placebo group. The estimated treatment difference was −0.83 points, in favour of THC/CBD spray, a highly statistically significant result compared with placebo ($p = 0.0072$; 95% CI: −1.43 to −0.23 points) (Table 3). In the PP population, the treatment difference was slightly greater, in favour of THC/CBD spray, and was also statistically significant compared with placebo (−0.91 points, $p = 0.015$; 95% CI: −1.63 to −0.18 points) (Table 3).

In the secondary efficacy analysis of SGIC, there was a statistically significant treatment difference in favour of THC/CBD spray in the ITT dataset, compared with placebo (odds ratio: 1.76; $p = 0.023$; 95% CI: 1.08–2.88) that was mirrored in the PP population, with the odds ratio in favour of THC/CBD spray increasing to 2.99 compared with placebo ($p = 0.0003$; 95% CI: 1.66, 5.38). The proportion of patients selecting each category is presented in Fig. 3.

Decreases (improvements) in favour of the THC/CBD spray group were also observed in the following parameters: NPS total score, mean number of tablets of rescue medication administered, BPI-SF scores (pain severity composite score, average pain, worst pain and pain interference composite score) and EQ-5D questionnaire scores (both weighted health status index VAS and self-rated health status VAS). These results applied to both ITT and PP population analysis sets, but none reached statistical significance (Table 2). The dynamic allodynia test score increased (improved) in the ITT analysis set but was not in favour of active treatment in the PP analysis set (Table 2).

Interestingly, there was an apparent treatment by centre interaction in the changes from baseline to the end of treatment in sleep quality 0–10 NRS ($p = 0.016$) and BPI-SF scores ($p = 0.079$) (in the domain of 'pain interference composite'), with an apparent treatment effect in the UK but not elsewhere (data not shown).

3.4 Safety and tolerability

All AEs experienced by patients with an incidence of 3% or greater during this study are displayed in Table 4. The most common system organ classes (SOCs) affected for treatment-related AEs were 'nervous system disorders', 'gastrointestinal disorders', 'general disorders and administration site conditions', 'infections and infestations' and 'psychiatric disorders'. 'Psychiatric disorders' were experienced by 36 (28%) patients receiving THC/CBD spray versus only 11 (9%) receiving placebo. By preferred term, dissociation [nine (7%) THC/CBD spray patients affected vs.

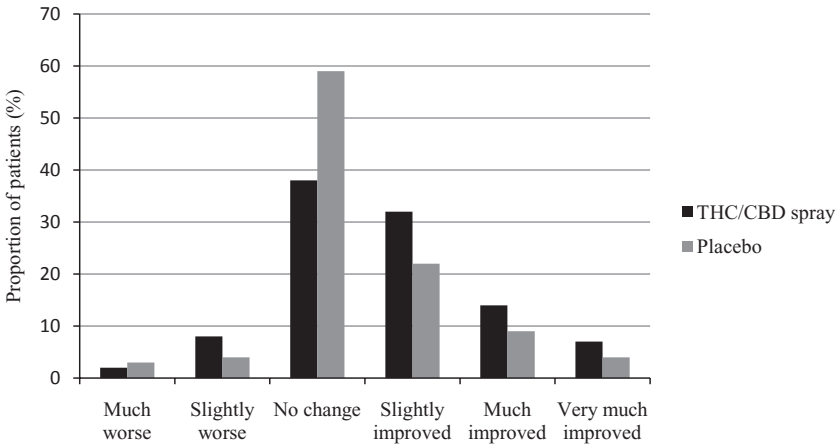

Figure 3 Subject global impression of change, intention-to-treat complete period.

no placebo patients] and disorientation [eight (6%) THC/CBD spray patients affected vs. no placebo patients] were the most commonly reported AEs in this SOC (Table 4). Additionally, other SOCs were more commonly affected in the THC/CBD spray versus placebo arms, notably 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions' (Table 4).

The majority of treatment-emergent AEs were mild to moderate in severity across both treatment groups. Ten patients (8%) receiving THC/CBD spray experienced SAEs, none of which was considered to be treatment-related. Six patients (5%) receiving placebo experienced a treatment-emergent SAE, one of which was considered related to treatment. A total of 33 patients stopped receiving study medication due to AEs, 25 in the THC/CBD spray arm and 8 in the placebo group. No obvious trends were shown for biochemistry, haematology or urinalysis, and no mean changes in blood pressure and pulse rate were observed from baseline to final visit. Furthermore, no patients died during the course of this study.

4. Discussion

Neuropathic pain is one of the most difficult types of pain to treat (The Committee for Medicinal Products for Human Use (CHMP), 2004), with fewer than half of treated patients receiving meaningful benefit from any pharmacological drug (Attal et al., 2006). The current study patients represented an especially resistant treatment group as they had not responded adequately to existing therapies, had a mean pain 0–10 NRS score of 4 or above, despite the majority currently taking analgesics for their neuropathic pain, and had a median duration of neuropathic pain of more than 3 years. In the face of such prolonged neuropathic pain, a new therapy faces enormous challenges to modify significantly the changes established within the nervous system. Despite these limiting factors, this study confirms the results previously reported, showing THC/CBD spray to produce a clinically relevant improvement (30% or more) in mean daily pain in a significantly greater proportion of patients than placebo when administered in addition to existing medication (Nurmikko et al., 2007). Furthermore, since the evidence base is considered to be poor for medicines currently licensed for the treatment of evoked neuropathic phenomena, these findings suggest that THC/CBD spray is a promising new candidate for treating mixed neuropathic pain characterized by allodynia (Rowbotham et al., 1998). An additional advantage of THC/CBD oromucosal spray is the simple handling and fast action of the medicament.

A greater than 30% improvement in pain intensity, considered to signify a clinically meaningful improvement (Rasmussen et al., 2004), was reported by 28% of patients receiving THC/CBD spray compared with 16% of patients taking placebo. This finding was statistically significant in favour of THC/CBD spray and, considering the patient population in the study, is encouraging. The co-primary analysis of the mean change from baseline to the end of treatment in PNP 0–10 NRS score also showed a treatment difference in favour of THC/CBD spray, but this did not reach statistical significance.

The importance of sleep in chronic pain states has been well established (Casarett et al., 2001; Turk and Dworkin, 2004), and improved sleep is considered a significant treatment objective by patients (Dworkin et al., 2005), especially as neuropathic pain tends to be worse at night (Stacey et al., 2010). Here, we demonstrate a statistically significant improvement in sleep with THC/CBD spray treatment, a finding that sup-

Table 4 Number of patients with at least one all-causality or treatment-related AE with an incidence of 3% or greater by primary system organ class and preferred term (as medically encoded using the Medical Dictionary for Regulatory Activities [MedDRA] version 8.1).

System organ class Preferred term	All-causality		Treatment-related	
	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)	THC/CBD spray (*n* = 128)	Placebo (*n* = 118)
	No. of patients (%)		No. of patients (%)	
Total subjects with at least one AE	109 (85)	83 (70)	97 (76)	56 (47)
Nervous system disorders	79 (62)	34 (29)	73 (57)	20 (17)
Dizziness	52 (41)	12 (10)	50 (39)	11 (9)
Dysgeusia	14 (11)	2 (2)	14 (11)	2 (2)
Headache	13 (10)	9 (8)	8 (6)	7 (6)
Disturbance in attention	8 (6)	2 (2)	8 (6)	1 (1)
Neuropathy peripheral	6 (5)	4 (3)	3 (2)	0
Tremor	6 (5)	0	4 (3)	0
Somnolence	5 (4)	2 (2)	5 (4)	2 (2)
Balance disorder	4 (3)	2 (2)	4 (3)	2 (2)
Memory impairment	4 (3)	2 (2)	4 (3)	2 (2)
Sedation	4 (3)	0	4 (3)	0
Gastrointestinal disorders	60 (47)	43 (36)	48 (38)	30 (25)
Nausea	23 (18)	14 (12)	22 (17)	9 (8)
Vomiting	13 (10)	7 (6)	6 (5)	3 (3)
Diarrhoea	12 (9)	6 (5)	8 (6)	2 (2)
Dry mouth	11 (9)	4 (3)	11 (9)	4 (3)
Abdominal pain upper	6 (5)	1 (1)	4 (3)	0
Dyspepsia	6 (5)	4 (3)	1 (1)	3 (3)
Constipation	4 (3)	2 (2)	2 (2)	0
Mouth ulceration	4 (3)	6 (5)	4 (3)	6 (5)
Oral pain	4 (3)	3 (3)	4 (3)	3 (3)
General disorders and administration site conditions	45 (35)	30 (25)	38 (30)	23 (19)
Fatigue	20 (16)	8 (7)	19 (15)	5 (4)
Feeling drunk	8 (6)	3 (3)	8 (6)	3 (3)
Application site pain	7 (5)	2 (2)	7 (5)	2 (2)
Psychiatric disorders	36 (28)	11 (9)	30 (23)	4 (3)
Dissociation	9 (7)	0	9 (7)	0
Disorientation	8 (6)	0	8 (6)	0
Depression	6 (5)	0	3 (2)	0
Anxiety	4 (3)	1 (1)	3 (2)	1 (1)
Panic attack	4 (3)	1 (1)	3 (2)	0
Infections and infestations	35 (27)	26 (22)	1 (1)	3 (3)
Nasopharyngitis	9 (7)	8 (7)	1 (1)	1 (1)
Gastroenteritis	4 (3)	1 (1)	0	0
Lower Respiratory Tract Infection	4 (3)	3 (3)	0	0
Metabolism and nutrition disorders	15 (12)	6 (5)	10 (8)	5 (4)
Increased appetite	6 (5)	1 (1)	6 (5)	1 (1)
Anorexia	4 (3)	1 (1)	1 (1)	1 (1)
Respiratory, thoracic and mediastinal disorders	15 (12)	16 (14)	7 (5)	5 (4)
Pharyngolaryngeal pain	7 (5)	5 (4)	2 (2)	5 (4)
Dyspnoea	4 (3)	3 (3)	1 (1)	0
Musculoskeletal and connective tissue disorders	11 (9)	8 (7)	2 (2)	1 (1)
Injury, poisoning and procedural complications	9 (7)	6 (5)	2 (2)	0
Skin and subcutaneous tissue disorders	9 (7)	9 (8)	2 (2)	2 (2)
Rash	5 (4)	4 (3)	1 (1)	0
Eye disorders	7 (5)	6 (5)	5 (4)	3 (3)
Ear and labyrinth disorders	6 (5)	1 (1)	5 (4)	1 (1)
Vertigo	5 (4)	0	5 (4)	0
Vascular disorders	4 (3)	5 (4)	3 (2)	2 (2)
Investigations	3 (2)	3 (3)	2 (2)	2 (2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (2)	1 (1)	0	0
Renal and urinary disorders	3 (2)	2 (2)	0	1 (1)
Cardiac disorders	2 (2)	2 (2)	1 (1)	0
Reproductive system and breast disorders	2 (2)	1 (1)	0	0
Immune system disorders	1 (1)	0	0	0
Blood and lymphatic system disorders	0	2 (2)	0	0

AE, adverse effect; CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol.

ports the consistent improvements in sleep seen in other clinical studies of this drug (Rog et al., 2005, 2007; Attal et al., 2006; Nurmikko et al., 2007). This provides further evidence for the efficacy of THC/CBD spray. Additionally, these improved sleep quality findings are also consistent with recent studies with smoked cannabis (Ware et al., 2010) and synthetic THC (Toth et al., 2012).

Analysis of the SGIC parameter evolution in the current study demonstrated a statistically significant treatment difference in favour of THC/CBD spray, with the most pronounced difference observed in the 'No Change' category, selected by a relatively high proportion of patients in the placebo group. The SGIC tool is considered the 'gold standard' measure of patient outcome in chronic pain trials (Dworkin et al., 2005). Based on this, our findings suggest that overall, patients can achieve important changes in quality of life with THC/CBD spray treatment.

Interestingly, other cannabinoid trials in which evoked pain was assessed reported some similar benefits to the current study (Svendsen et al., 2004; Abrams et al., 2007; Ware et al., 2010; Toth et al., 2012). Two RCTs that evaluated the effects of smoked cannabis on post-traumatic, post-surgical neuropathic pain (Ware et al., 2010) or HIV-associated sensory pain (Abrams et al., 2007) both demonstrated benefits in levels of pain intensity with active treatment. A further two trials that investigated different synthetic forms of THC, dronabinol (Svendsen et al., 2004) and nabilone (Toth et al., 2012) in the treatment of evoked pain, again demonstrated benefits in levels of pain intensity, as well as improvements in the quality of life and overall patient status, which is similar to the current study.

All other secondary endpoints that directly measured pain intensity showed improvements from baseline to the end of treatment, with treatment differences in favour of THC/CBD spray compared with placebo treatment, with only one exception. The punctate allodynia test score was found to improve with THC/CBD spray treatment, but the treatment difference was in favour of placebo. The analysis of rescue analgesia use also showed a tendency for reduced use in the THC/CBD spray treatment group compared with placebo, which could have impacted the pain questionnaire outcomes.

Throughout this study, existing analgesia was maintained based on ethical and clinical considerations. A variety of treatments for neuropathic pain have demonstrated efficacy and are in widespread use based on existing guidelines (Attal et al., 2006). To deprive a patient of these treatments during a placebo-controlled trial would not be ethical. Moreover, the use of combination treatments in clinical practice is becoming more commonplace due to the understanding that multiple pain mechanisms contribute to neuropathic pain (Woolf, 2004; Wade et al., 2010). Adding THC/CBD spray to a mixture of pain treatments, which work by different mechanisms, should not impede the activity of THC/CBD spray. However, if the other treatments are providing partial pain relief, this could reduce the magnitude of benefit derived from THC/CBD spray. The patients recruited for this trial were often very resistant to pharmacological therapy, so to show a 30% improvement in pain intensity in a proportion of patients was a clinically significant achievement.

The self-titration regimen used was chosen for a number of reasons, including the variable threshold of individual patients to the pharmacodynamic effects of THC/CBD spray (Rog et al., 2005; Attal et al., 2006). Having a self-titration schedule allowed patients to optimize their dose based on their own efficacy and tolerability.

In terms of safety, THC/CBD spray was well tolerated in this study, with low levels of intoxication experienced, and no evidence of tolerance developing, since there was a stable dose pattern following initial titration. The most common treatment-emergent, treatment-related events were dizziness, nausea, fatigue and dysgeusia (distortion of sense of taste). These AEs have been observed in other clinical studies with THC/CBD spray and are recognized as having a possible causal relationship to the study medication (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). The increased incidence of AEs in certain SOCs with THC/CBD spray treatment compared with placebo (i.e., 'psychiatric disorders', 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions') have also been previously reported in other clinical trials with THC/CBD spray (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). Psychiatric events such as dissociation and disorientation are known to be common in clinical trials with THC/CBD spray and are representative of a cannabis 'high' (Wade, 2012). A review of 805 THC/CBD spray patients versus 741 placebo patients found that 4% taking THC/CBD spray versus 0.5% taking placebo experienced disorientation, while 1.7% taking THC/CBD spray versus 0.1% taking placebo experienced dissociation (Wade, 2012). While the incidence of these two specific AEs was higher in this study, this may have been due to the titration regimen adopted. Indeed, a slower up-titration administration regimen for THC/CBD spray (over a 10-day period) was associated with a

lower number of AEs in later studies (Collin et al., 2010; Novotna et al., 2011). In clinical trials of THC/CBD spray using a slow up-titration schedule, the incidence of psychiatric AEs is reduced from 15% to 8% compared with the original more aggressive regimen adopted in this study (Wade, 2012).

A total of 10 SAEs were experienced by patients receiving THC/CBD spray; however, none was considered to be treatment-related. There were no consistent patterns of difference between THC/CBD spray and placebo for haematology, biochemistry and urinalysis parameters. Furthermore, changes in vital signs for pulse rate and systolic blood pressure were unremarkable compared with baseline.

4.1 Study limitations

The presence of a substantial proportion of non-responders in this study suggests that the analysis of mean changes may not be the most appropriate means of identifying whether the medication has a clinically useful effect, since the lack of improvement in the non-responders would dilute the improvement seen in responders. In clinical practice, non-responders to treatment would be unlikely to remain on a non-effective drug and would therefore not contribute to understanding the utility of the medicine in the population of patients for whom it is suitable. This dilemma has been discussed by McQuay et al. (2008).

Another potential study limitation was the inclusion of multiple aetiologies of PNP leading to considerable clinical trial heterogeneity. The issue of clinical trial heterogeneity in patients with neuropathic pain has been well-documented, and several other controlled trials of promising new therapeutic candidates have been negative (Baron et al., 2012). By contrast, a variety of neuropathic pain studies in heterogeneous populations such as the current study have reported positive results in terms of pain scores (Serpell, 2002; Rowbotham et al., 2003), including studies in which vaporized cannabis (Wilsey et al., 2013) and cannabis cigarettes (Wilsey et al., 2008) were used, although slightly different pain scales were adopted than those used in the current study. Several clinical trials and post-hoc analyses have shown greater efficacy of the study drug when patients are sub-grouped based on baseline sensory symptoms and/or pain thresholds (Edwards et al., 2006; Simpson et al., 2010; Campbell et al., 2012). As such, future studies that incorporate sensory profiling may reveal specific subgroups of patients in which THC/CBD spray is efficacious.

A potential drawback of the maximum dose of 24 daily sprays adopted in this study was the potential for a 'placebo effect', which may have diminished the positive results seen with THC/CBD spray. While the treatment difference in favour of THC/CBD spray increased with increasing daily doses of study medication, this effect appeared to drop off at a dose of around 14–15 sprays per day. At a similar dose, however, the proportion of responders in the placebo treatment group was still increasing markedly with increasing numbers of daily sprays. This suggests that patients who took higher mean daily doses of placebo perceived a benefit in the subjective pain severity score. The consequence of this effect is an apparent decrease in the true treatment advantage of THC/CBD spray over placebo, observed at lower daily doses. These findings suggest that future studies would benefit from a reduction in the current dose ceiling of 24 sprays per day, thus allowing comparison of the two treatment groups at similar mean doses.

5. Conclusions

In conclusion, this study has shown that in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in their pain, sleep quality and global impression of change in the severity of their condition were obtained by taking THC/CBD spray. There is also a possibility that these results may have been more strongly in favour of THC/CBD spray if the upper dose level had been capped to below 24 sprays daily, and a slower titration regimen had been adopted in an attempt to improve the overall tolerability and its effect of early withdrawals and, secondarily, to reduce the placebo response. Reassuringly, there was no evidence of tolerance developing and few patients reported experiencing severe AEs. Taken together, these finding are encouraging and suggest that treatment of PNP associated with allodynia with THC/CBD spray could bring significant benefit to patients.

Author contributions

All authors made a substantial contribution to the acquisition and interpretation of the data, critically reviewed the article and approved the final version for publication.

References

Abrams, D.I., Jay, C.A., Shade, S.B., Vizoso, R.N., Reda, H., Press, S., Kelly, M.E., Rowbotham, M.C., Petersen, K.L. (2007). Cannabis in painful HIV-associated sensory neuropathy. A randomised placebo-controlled trial. *Neurology* 68, 515–521.

Attal, N., Cruccua, G., Haanpää, M., Hansson, P., Jensen, T.S., Nurmikko, T., Sampaio, C., Sindrup, S., Wiffen, P., EFNS Task Force. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 13(11), 1153–1169.

Backonja, M., Serra, J. (2004). Pharmacologic management part 1: Better studied neuropathic pain diseases. *Pain Med* 5, S28–S47.
Baron, R., Förster, M., Binder, A. (2012). Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: A first step to a stratified treatment approach. *Lancet Neurol* 11(11), 999–1005.
Berman, J.S., Symonds, C., Birch, R. (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomized controlled trial. *Pain* 112, 299–306.
Bouhassira, D., Lanteri-Minet, M., Attal, N., Laurent, B., Touboul, C. (2008). Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 136, 380–387.
Boureau, F., Legallicier, P., Kabir-Ahmadi, M. (2003). Tramadol in post-herpetic neuralgia: A randomised, double-blind, placebo-controlled trial. *Pain* 104, 323–331.
Campbell, C.M., Kipnes, M.S., Stouch, B.C., Brady, K.L., Kelly, M., Schmidt, W.K., Petersen, K.L., Rowbotham, M.C., Campbell, J.N. (2012). Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. *Pain* 153(9), 1815–1823.
Casarett, D., Karlawish, J., Sankar, P., Hirschman, K., Asch, D.A. (2001). Designing pain research from the patients' perspective: What trial end-points are important to patients with chronic pain? *Pain Med* 2, 309–316.
Cleeland, C.S., Ryan, K.M. (1994). Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 23(2), 129–138.
Collin, C., Ehler, E., Waberzinek, G., Alsindi, Z., Davies, P., Powell, K., Notcutt, W., O'Leary, C., Ratcliffe, S., Nováková, I., Zapletalova, O., Piková, J., Ambler, Z. (2010). A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res* 32(5), 451–459.
Dworkin, R.H., Turk, D.C., Farrar, J.T., Haythornewaite, J.A., Jensen, M.P., Katz, N.P., Kerns, R.D., Stucki, G., Allen, R.R., Bellamy, N., Carr, D.B., Chandler, J., Cowan, P., Dionne, R., Galer, B.S., Hertz, S., Jadad, A.R., Kramer, L.D., Manning, D.C., Martin, S., McCormick, C.G., McDermott, M.P., McGrath, P., Quessy, S., Rappaport, B.A., Robbins, W., Robinson, J.P., Rothman, M., Royal, M.A., Simon, L., Stauffer, J.W., Stein, W., Tollett, J., Wernicke, J., Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113, 9–19.
Edwards, R.R., Haythornthwaite, J.A., Tella, P., Max, M.B., Raja, S. (2006). Basal heat pain thresholds predict opioid analgesia in patients with postherpetic neuralgia. *Anesthesiology* 104(6), 1243–1248.
Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 54(2), 161–202.
Jensen, T.S., Gottrup, H., Sindrup, S.H., Bach, F.W. (2001). The clinical picture of neuropathic pain. *Eur J Pharmacol* 429, 1–11.
Karst, M., Salim, K., Burstein, S., Conrad, I., Hoy, L., Schneider, U. (2003). Analgesic effect of the synthetic cannabinoid CT3 on chronic neuropathic pain. A randomized controlled trial. *JAMA* 290(13), 1757–1762.
McQuay, H.J., Derry, S., Moore, R.A., Poulain, P., Legout, V. (2008). Enriched enrolment with randomised withdrawal (EERW): Time for a new look at clinical trial design in chronic pain. *Pain* 135, 217–220.
MHRA Public Assessment Report. (2010). Nabiximols Oromucosal Spray (delta-9-tetrahydrocannabinol and cannabidiol) – PL 18024/0009. UK/H/2462/001/DC. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf (accessed January 2012).
Novotna, A., Mares, J., Ratcliffe, S., Novakova, I., Vachova, M., Zapletalova, O., Gasperini, C., Pozzilli, C., Cefaro, L., Comi, G., Rossi, P., Ambler, Z., Stelmasiak, Z., Erdmann, A., Montalban, X., Klimek, A., Davies, P., Sativex Spasticity Study Group. (2011). A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 18, 1122–1131.
Nurmikko, T.J., Serpell, M.G., Hoggart, B., Toomey, P.J., Morlion, B.J., Haines, D. (2007). Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* 133, 210–220.
Rasmussen, P.V., Sindrup, S.H., Jensen, T.S., Bach, F.W. (2004). Therapeutic outcome in neuropathic pain: Relationship to evidence of nervous system lesion. *Eur J Neurol* 11, 545–553.
Rice, A.S., Maton, S.; Postherpetic Neuralgia Study Group. (2001). Gabapentin in post herpetic neuralgia: A randomised, double blind, placebo controlled study. *Pain* 94(2), 215–224.
Rog, D.J., Nurmikko, T.J., Friede, T., Young, C.A. (2005). Randomized controlled trial of cannabis based medicine in central pain due to multiple sclerosis. *Neurology* 65, 812–819.
Rog, D.J., Nurmikko, T.J., Young, C.A. (2007). Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial. *Clin Ther* 29(9), 2068–2079.
Rowbotham, M., Harden, N., Stacey, B., Bernstein, P., Magnus-Miller, L. (1998). Gabapentin for the treatment of post herpetic neuralgia. *JAMA* 280, 1837–1842.
Rowbotham, M.C., Twilling, L., Davies, P.S., Reisner, L., Taylor, K., Mohr, D. (2003). Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 348(13), 1223–1232.
Russo, E.B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* 163(7), 1344–1364.
Serpell, M.G., Neuropathic Pain Study Group. (2002). Gabapentin in neuropathic pain syndromes: A randomised, double-blind, placebo-controlled trial. *Pain* 99, 557–566.
Simpson, D.M., Schifitto, G., Clifford, D.B., Murphy, T.K., Durso-De Cruz, E., Glue, P., Whalen, E., Emir, B., Scott, G.N., Freeman, R., 1066 HIV Neuropathy Study Group. (2010). Pregabalin for painful HIV neuropathy: A randomized, double-blind, placebo-controlled trial. *Neurology* 74(5), 413–420.
Stacey, B.R., Dacosta DiBonaventura, M., Martin, S., Bell, C.F. (2010). Chronological Characteristics of Painful Diabetic Peripheral Neuropathy. American Pain Society ASM, Abstract 23.
Svendsen, K.B., Jensen, T.S., Bach, F.W. (2004). Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 329, 253–260.
The Committee For Medicinal Products For Human Use (CHMP). Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment Of Neuropathic Pain London, 18 November 2004 CHMP/EWP/252/03.
The Euroqol Group. (1990). Euroqol – a new facility for the measurement of health-related quality of life. *Health Policy* 16, 199–208.
Torrance, N., Smith, B.H., Bennett, M.I., Lee, A.J. (2006). The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *Pain* 7, 281–289.
Toth, C., Mawani, S., Brady, S., Chan, C., Liu, C., Mehina, E., Garven, A., Bestard, J., Korngut, L. (2012). An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 153(10), 2073–2082.
Turk, D.C., Dworkin, R.H. (2004). What should be the core outcomes in chronic pain clinical trials? *Arthritis Res Ther* 6, 151–154.
Wade, D. (2012). Evaluation of the safety and tolerability profile of Sativex: Is it reassuring enough? *Expert Rev Neurother* 12(4 Suppl), 9–14.
Wade, D.T., Collin, C., Stott, C., Duncombe, P. (2010). Meta-analysis of the efficacy and safety of Sativex (nabiximols) on spasticity in people with multiple sclerosis. *Mult Scler* 16, 707–714.
Ware, M.A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., Gamsa, A., Bennett, G.J., Collet, J.P. (2010). Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 182(14), E694–E701.
Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., Donaghe, H. (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* 14(2), 136–148.
Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 9(6), 506–521.
Woolf, C.J. (2004). Dissecting out mechanisms responsible for peripheral neuropathic pain: Implications for diagnosis and therapy. *Life Sci* 74, 2605–2610.
Woolf, C.J., Max, B.M. (2001). Mechanism-based pain diagnosis. *Anaesthesiology* 95, 241–249.

Clinical Review

Pharmacologic management of chronic neuropathic pain

Review of the Canadian Pain Society consensus statement

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Abstract

Objective To provide family physicians with a practical clinical summary of the Canadian Pain Society (CPS) revised consensus statement on the pharmacologic management of neuropathic pain.

Quality of evidence A multidisciplinary interest group within the CPS conducted a systematic review of the literature on the current treatments of neuropathic pain in drafting the revised consensus statement.

Main message Gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors are the first-line agents for treating neuropathic pain. Tramadol and other opioids are recommended as second-line agents, while cannabinoids are newly recommended as third-line agents. Other anticonvulsants, methadone, tapentadol, topical lidocaine, and botulinum toxin are recommended as fourth-line agents.

Conclusion Many pharmacologic analgesics exist for the treatment of neuropathic pain. Through evidence-based recommendations, the CPS revised consensus statement helps guide family physicians in the management of patients with neuropathic pain.

EDITOR'S KEY POINTS

- Gabapentinoids and tricyclic antidepressants play an important role in first-line management of neuropathic pain (NeP). Evidence published since the 2007 Canadian Pain Society consensus statement on treatment of NeP shows that serotonin-norepinephrine reuptake inhibitors should now also be among the first-line agents.
- Tramadol and opioids are considered second-line treatments owing to their increased complexity of follow-up and monitoring, plus their potential for adverse side effects, medical complications, and abuse. Cannabinoids are currently recommended as third-line agents, as sufficient-quality studies are currently lacking. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol, and botulinum toxin. There is some support for analgesic combinations in selected NeP conditions.
- Many of these pharmacologic treatments are off-label for pain or on-label for specific pain conditions, and these issues should be clearly conveyed and documented.

POINTS DE REPÈRE DU RÉDACTEUR

- Les gabapentinoïdes et les antidépresseurs tricycliques jouent un rôle important dans la prise en charge de la douleur neuropathique en soins primaires. Des données probantes publiées depuis la déclaration consensuelle de la Société canadienne de la douleur en 2007 sur le traitement de la douleur neuropathique démontrent que les inhibiteurs de la recapture de la sérotonine et de la noradrénaline devraient aussi compter parmi les agents de première intention.
- Le tramadol et les opioïdes sont considérés comme des traitements de deuxième intention en raison de la complexité du suivi et de la surveillance, sans compter leur potentiel d'effets secondaires indésirables, de complications médicales et d'usage abusif. Les cannabinoïdes sont présentement recommandés comme agents de troisième intention, étant donné l'absence actuelle d'études de qualité suffisante. Parmi les traitements de quatrième intention recommandés figurent la méthadone, les anticonvulsivants dont l'efficacité est corroborée par moins de données probantes (p. ex. lamotrigine, lacosamide), le tapentadol et la toxine botulique. Le recours à une combinaison d'analgésiques reçoit un certain appui dans des cas particuliers de douleur neuropathique.
- L'utilisation de bon nombre de ces pharmacothérapies est non indiquée pour la douleur ou encore est indiquée pour des problèmes de douleur spécifiques. Ces faits devraient être clairement communiqués et documentés.

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Cet article a fait l'objet d'une révision par des pairs.
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Prise en charge pharmacologique de la douleur neuropathique chronique

Revue de la déclaration consensuelle de la Société canadienne de la douleur

Résumé

Objectif Offrir aux médecins de famille un résumé clinique pratique de la déclaration consensuelle révisée de la Société canadienne

de la douleur (SCD) sur la prise en charge pharmacologique de la douleur neuropathique.

Qualité de l'information Un groupe d'intérêt multidisciplinaire au sein de la SCD a effectué une revue systématique des ouvrages scientifiques sur les traitements actuels de la douleur neuropathique dans le contexte de la rédaction d'une déclaration consensuelle révisée.

Message principal Les gabapentinoïdes, les antidépresseurs tricycliques, et les inhibiteurs de la recapture de la sérotonine et de la noradrénaline sont les agents de première intention pour traiter la douleur neuropathique. Le tramadol et les autres opioïdes sont recommandés comme agents de deuxième intention, tandis que les cannabinoïdes sont recommandés depuis peu comme agents de troisième intention. D'autres anticonvulsivants – la méthadone, le tapentadol, la lidocaïne topique et la toxine botulique – sont recommandés comme agents de quatrième intention.

Conclusion Il existe de nombreux analgésiques pharmacologiques pour le traitement de la douleur neuropathique. Par ses recommandations fondées sur des données probantes, la déclaration consensuelle révisée de la SCD aide à orienter les médecins de famille dans la prise en charge des patients souffrant de douleur neuropathique.

Neuropathic pain (NeP), caused by a lesion or disease of the somatosensory system, is a common condition seen in the primary care setting. Although the prevalence of NeP is estimated to be 2% to 3% in the developed world, population-based questionnaires estimate that the prevalence could actually be in the range of 4% to 8%.[1,2] The prevalence of NeP will increase over the next decades as our population ages and experiences more obesity. This has led to increased rates of postherpetic neuralgia and painful diabetic neuropathy.[3,4] Improved cancer screening and treatments are also leading to more cancer survivors experiencing NeP from various medical and surgical oncologic interventions.[5]

The goals of treatment of NeP, as with other pain conditions, include improvement in function and quality of life, along with the reduction of pain. The ideal treatment of NeP should entail a whole-person approach (biological, psychological, social, spiritual), be multidisciplinary in nature, include prevention or reversal of any underlying cause, and use appropriate pharmacologic and nonpharmacologic therapies. As first-line personnel in the treatment of NeP, primary care clinicians need to be aware of current Canadian guidance on the pharmacologic treatment of NeP so that an appropriate and rational stepwise approach is implemented. The primary aim of this article is to highlight the revised neuropathic pain medication algorithm that was created by a panel of experts within the Canadian Pain Society (CPS).

Consensus statement development

The Neuropathic Pain Special Interest Group of the CPS began meeting in 2012 to update the 2007 pharmacologic management guidelines for NeP.[6] This interest group is a multidisciplinary group of individuals with research and clinical expertise relevant to the pathophysiology and management of NeP. Randomized controlled trials (RCTs) and systematic reviews related to the pharmacologic management of NeP from 2007 up to September 2013 were reviewed to develop a revised evidence-based consensus statement.[7]

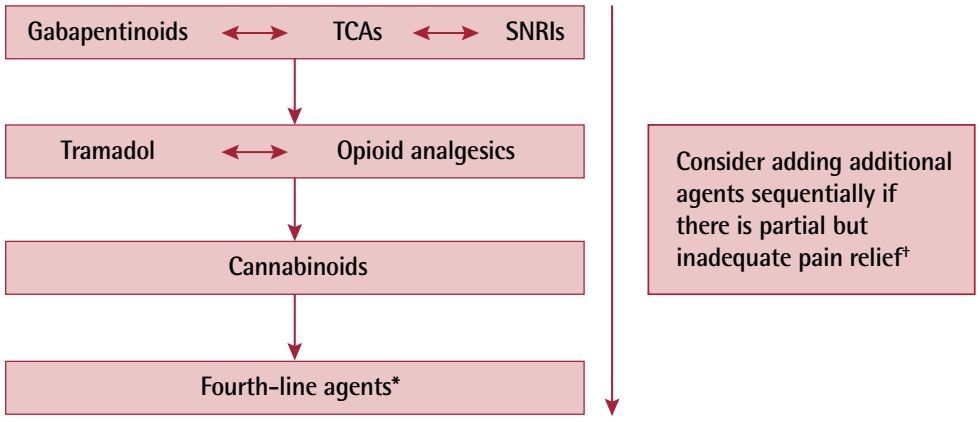
Quality of evidence

As per the published report,[7] MEDLINE and Cochrane databases were used to find systematic reviews, meta-analyses, treatment recommendations, guidelines, and consensus statements published since the first 2007 CPS consensus statement. Studies were excluded if they did not have a control group, had fewer than 10 patients, involved trigeminal or glossopharyngeal neuralgia, or involved cancer NeP, except for well-defined cancer-related postsurgical pain syndromes and chemotherapy-induced NeP. Medications were considered to be first-line if there was high-quality evidence of efficacy (at least 1 class I study or 2 consistent class II studies—level of recommendation grade B or better),[8] if there were positive results in at least 2 NeP models,[9] and if they were considered to be straightforward and of sufficient tolerability to prescribe and monitor. Second- or third-line medications require high-quality evidence of efficacy, but the medications also require more specialized follow-up and monitoring. Fourth-line treatments have at least 1 RCT with positive results, but require further study.

Main message

Neuropathic pain is a common condition seen in the family practice setting in Canada. **Figure 1** summarizes the revised 2014 CPS consensus statement for pharmacologic management of NeP.[7] Gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are now recommended as first-line agents. Tramadol and opioids are considered second-line treatments owing to their increased complexity of follow-up and monitoring, plus their potential for adverse side effects, medical complications, and abuse. Cannabinoids are currently recommended as third-line agents, as sufficient-quality studies are currently lacking. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol, and botulinum toxin. There is some support for analgesic combinations in selected NeP conditions.

Figure 1. Algorithm for the pharmacologic management of neuropathic pain



SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant.
*Fourth-line agents include topical lidocaine (second-line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, and botulinum toxin.
†There is limited randomized controlled trial evidence to support add-on combination therapy.
Adapted from Moulin et al.[7]

Many of these pharmacologic treatments are off-label for pain or on-label for specific pain conditions, and these issues should be clearly conveyed and documented.

Assessment and diagnosis of NeP. Neuropathic pain can be mediated by central causes, such as stroke or multiple sclerosis, and by peripheral causes, such as diabetic neuropathy or surgical procedures. The patient's history and physical examination findings are essential to diagnosing NeP. Some diagnoses based on history are obvious, such as shingles and diabetes mellitus preceding postherpetic neuralgia and painful diabetic neuropathy, respectively. Questionnaires have been developed to help differentiate between nociceptive pain and NeP. True weakness (different from pain-related or antalgic weakness), reduced or absent reflexes, allodynia, and hyperalgesia all favour a diagnosis of NeP. Often patients describe neuropathic pain as accompanied by sensations of burning, tingling, and electric jolts. Screening tools, such as the Douleur Neuropathique 4, the self-report Leeds Assessment of Neuropathic Symptoms and Signs, and the ID Pain questionnaire (**Table 1**), have been shown to be valid and reliable discriminators of NeP.[10-12] Electromyography and nerve conduction studies can provide evidence of nerve injury but might not be sensitive for small-fibre neuropathies. Guidelines are available to determine the diagnostic certainty of NeP.[13,14]

CanMEDS–Family Medicine considerations. Chronic pain conditions, such as NeP, require management by physicians using more than pharmacologic expertise. The CanMEDS–Family Medicine roles described by the College of Family Physicians of Canada serve as a framework for improving patient care.[15] Specifically, as professionals, physicians must commit to regulated, ethical practice with high personal standards of behaviour. Being a scholar requires lifelong commitment to learning, creation, dissemination, and translation of medical pain knowledge. As family medicine experts, the knowledge is applied in a manner that places patients and families in the correct biopsychosocial-spiritual framework within their community. Patients with chronic pain experiencing NeP often describe this condition as severe and unrelenting, and it is often associated with comorbid anxiety and depression. As a communicator, the practitioner should facilitate the doctor-patient relationship through validation of the patient's pain and communicate the treatment goals, such as improvement of

Table 1. ID Pain questions and scoring: *If patients have >1 painful area, they are to consider the area that is most relevant when answering the ID Pain questions. Scores range from -1 to 5. Higher scores are more indicative of pain with a neuropathic component.*

QUESTION	SCORE	
	YES	NO
1. Did the pain feel like pins and needles?	1	0
2. Did the pain feel hot or burning?	1	0
3. Did the pain feel numb?	1	0
4. Did the pain feel like electrical shocks?	1	0
5. Is the pain made worse with the touch of clothing or bed sheets?	1	0
6. Is the pain limited to your joints?	-1	0

Adapted from Portenoy.[12]

sleep, physical functioning, and other elements of quality of life, and discuss pain reduction such that the pain might become "tolerable," rather than promise the elimination of the pain condition. Patients should be made aware that chronic pain might be a lifelong condition. As a collaborator and leader, treatment goals can be realized by involving multidisciplinary teams (psychologists, physiotherapists, etc) to maximize nonpharmacologic adjunctive treatments. Family physicians serve as their patients' main advocate within their communities, and help them to navigate the health care system.

First-line analgesics. The first-line medications are the gabapentinoid class of anticonvulsants, TCAs, and SNRIs. There are positive results showing efficacy in painful diabetic neuropathy for all first-line analgesics.[16-19] In the context of postherpetic neuralgia, there has been proof of efficacy for gabapentinoids and TCAs.[16,18] Pregabalin has additionally been shown to have analgesic benefit in patients with chronic central NeP after spinal cord injury[20,21] and secondary benefit (improved sleep and reduced anxiety) in central poststroke pain.[22] Tricyclic antidepressants have been shown to relieve pain in various NeP conditions.[23] Of the SNRIs, duloxetine has been found to have analgesic benefit in chemotherapy-induced painful neuropathy,[24] while gabapentin has been shown not to.[25] Additionally, high-dose venlafaxine has shown efficacy in mixed painful polyneuropathy.[26] In the context of idiopathic trigeminal neuralgia, an exception can be made for carbamazepine, which remains the first-choice analgesic.[27] Dosing guidelines for selected NeP analgesia agents can be found in **Table 2**.[7]

Tricyclic antidepressants are extensively studied, inexpensive, and administered daily. They inhibit the reuptake of serotonin and norepinephrine, block *N*-methyl-D-aspartate agonist–induced hyperalgesia, and block sodium channels.[28] When prescribing TCAs, secondary amines (nortriptyline, desipramine) are usually better tolerated in terms of sedation, postural hypotension, and anticholinergic effects when compared with tertiary amines (amitriptyline and imipramine) with comparable analgesic efficacy.[29] Side effects might also be reduced by starting at a lower dose, administration in the early evening, and titrating slowly. The analgesic effect of TCAs is independent of the antidepressant effect and the analgesic effect occurs at one-fifth to one-third of the dose required to treat depression.[30] In the geriatric population, TCAs might be deleterious, as they can impair cognition and increase the risk of falls.[31] The updated American Geriatrics Society Beers criteria and version 2 of the STOPP/START (Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment) criteria are useful references to minimize inappropriate prescribing in the elderly.[32,33] As TCAs have been associated with tachycardia and myocardial infarction (at doses above 100 mg daily), the Special Interest Group on Neuropathic Pain (NeuPSIG) recommends a baseline electrocardiogram in patients starting TCAs who are older than 40 years of age and are at risk of sudden cardiac death or who have a history of cardiovascular disease.[31]

Gabapentinoids lead to reduction of the influx of calcium in the terminals of primary afferent neurons entering the dorsal horn of the spinal cord.[28] Gabapentin and pregabalin are not hepatically metabolized, and they do not alter hepatic enzymes. As they are eliminated renally, dose adjustment is required in those with renal insufficiency or those who are undergoing dialysis.[34] Pregabalin can be taken twice a day and has more linear pharmacokinetics relative to gabapentin, which is taken 3 times a day. Somnolence, dizziness, edema, and weight gain are common side effects of gabapentinoids, and they might require low initial dosing and slow titration, especially in the elderly.[35]

Serotonin-norepinephrine reuptake inhibitors inhibit the reuptake of serotonin and norepinephrine at neuronal junctions. Duloxetine and venlafaxine are the 2 most studied drugs within this class. A typical side effect of duloxetine and venlafaxine is nausea; other side effects such as elevated heart rate and blood pressure are less common. Gastrointestinal side effects are most common with venlafaxine. Hepatotoxicity has been reported with duloxetine. Duloxetine directly relieves painful physical symptoms, in addition to the pain relief from improved depressive symptoms over time.[35,36] There is 1 phase III clinical trial of desvenlafaxine in the setting of NeP; at interim analysis, randomization to a 400-mg daily dose was discontinued owing to a clear increase in adverse events.[37] Duloxetine inhibits serotonin to norepinephrine reuptake at a ratio of 9:1 while venlafaxine has a ratio of 30:1.[38] At low doses (<200 mg daily), venlafaxine only inhibits serotonin.[39] There is evidence that combination pharmacotherapy with gabapentinoids and SNRIs can be helpful.[35] Duloxetine should be avoided in those with hepatic insufficiency and severe renal impairment; doses higher than 60 mg daily have not consistently shown benefit in clinical trials.[40] Tricyclic antidepressants, SNRIs, and selective serotonin reuptake inhibitors are all relatively contraindicated with concurrent use of monoamine oxidase inhibitors owing to the possibility of serotonin syndrome.[41]

If patients are appropriately identified as having NeP using standardized NeP tools, first-line medications are very effective early in the treatment process.[42] The quality of the evidence provided above is high for SNRIs and gabapentinoids in the treatment of NeP, but moderate for TCAs if started before opioids.[42] A reduction in pain of 20% to 30% should be considered a success. A change in a patient's function, sleep pattern, or their ability to be social are key matters of evaluation rather than a pain numeric rating scale score.

Table 2. Selected neuropathic analgesic dosing regimens

AGENT	INITIAL DOSE	TITRATION	DOSE RANGE	ADVERSE EFFECTS	ADDITIONAL INFORMATION
Anticonvulsants					
• Gabapentin	100-300 mg/d	Increase by 100-300 mg/d every wk	300-1200 mg 3 times/d	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
• Pregabalin	25-150 mg/d	Increase by 25-150 mg/d every wk	150-300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
• Carbamazepine	100 mg/d	Increase by 100-200 mg/d every wk	200-400 mg 3 times/d	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for idiopathic trigeminal neuralgia; as an enzyme inducer, it might interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function recommended
TCAs					
• Amitriptyline, nortriptyline, or desipramine	10–25 mg/d	Increase by 10 mg/d every wk	10-100 mg/d	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism, and substantial cardiovascular disease
SNRIs					
• Venlafaxine	37.5 mg/d	Increase by 37.5 mg/d every wk	150-225 mg/d	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
• Duloxetine	30 mg/d	Increase by 30 mg/d every wk	60-120 mg/d	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Controlled-release opioids*					
• Morphine	15 mg every 12 h	NA	NA	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for overdose, effectiveness, tolerance, dependence, and appropriateness
• Oxycodone	10 mg every 12 h	NA	NA		
• Fentanyl	12 µg/h (patch)	NA	NA		
• Hydromorphone	3 mg every 12 h	NA	NA		
Others					
• Tramadol	50 mg/d	Increase by 50 mg/d every wk	50-100 mg 4 times/d or 100-400 mg/d (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypertension	Might lower seizure threshold; use with caution in patients with epilepsy
• Tapentadol (controlled release)	50 mg every 12 h	Increase by 50 mg/ dose every wk	Maximum dose 500 mg in 24 h	Nausea, constipation, somnolence, dizziness, vomiting, fatigue	Contraindicated in patients with creatinine clearance < 0.5 mL/s/m^2 and Child-Pugh class C. Caution in those at risk of seizure
• Lidocaine	NA	NA	5% patches or gel applied to painful areas for 12 h in a 24-h period	NA	Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
• THC or nabiximols	1-2 sprays every 4 h, maximum 4 sprays on day 1	NA	2 sprays 4 times/d	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug test results for cannabinoids; monitor application site (oral mucosa)
• Nabilone	0.25–0.5 mg at night (owing to side effects of drowsiness and fatigue)	Increase by 0.5 mg/d every wk	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not cause positive test results for cannabinoids on routine urine drug testing

NA—not available, SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant, THC—tetrahydrocannabinol.
*Opioid initial dosing recommendations are for healthy opioid-naïve adults; opioid titration and dose range are not included owing to variability of patient and pain factors.
Adapted with permission from Moulin et al.[7]

However, once opioid medications are entrenched, the effect sizes of these first-line medications tend to be minimized.

Second-line analgesics. Tramadol is a second-line medication in the treatment of NeP and has been shown to be of benefit in RCTs for diabetic neuropathy and mixed NeP syndromes.[18] It is a weak μ-opioid receptor agonist and weak SNRI.[43] The NeuPSIG also recommends it as a second-line agent.[42] Tramadol might cause less constipation and nausea compared with other weak analgesics.[44] Along with common opioid side effects, tramadol can decrease seizure thresholds and can increase the risk of serotonin syndrome when combined with other serotonergic drugs.[31]

Opioids were found to be more effective than placebo for pain, with a moderate effect size, in a meta-analysis including 16 randomized trials for chronic NeP.[45] However, owing to their potential adverse effects, medical complications (endocrine dysfunction, sleep apnea, opioid-induced hyperalgesia), risks (overdose, diversion, addiction, withdrawal), and necessity of more specialized follow-up and monitoring, opioids are considered to be second-line agents for NeP (**Table 3**).[46] In the recent NeuPSIG systematic review and meta-analysis, opioids are recommended as third-line analgesics for the same reasons.[42]

A meta-analysis of 62 RCTs found that the most common opioid-related adverse effects were nausea (28%), constipation (25%), drowsiness (24%), dizziness (18%), and vomiting (15%).[45] Although some tolerance to side effects develops, there is little tolerance to constipation in prolonged use. Long-term opioid use complications include opioid-induced hyperalgesia[47] and multiple endocrine axis suppression such as adrenal and gonadal suppression.[48] The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain is strongly recommended as a resource for family physicians.[46] An online and mobile resource, My Opioid Manager, is recommended to help inform and engage patients to work with their health care providers in managing their pain with opioids.[49] Another mobile app, Manage My Pain, has more than 25 000 active users and is used in chronic pain to empower the physician-patient relationship.[50]

Third-line analgesics. Cannabinoids have been moved from a fourth-line to a third-line treatment option for chronic NeP in the 2014 CPS NeP guidelines.[7] The strongest evidence for cannabinoid use is for NeP from HIV, diabetic neuropathy, posttraumatic or postsurgical NeP, and mixed central and peripheral NeP states.[51-55] However, there is a paucity of high-quality studies with long trial duration, large sample size, and large effect size to better establish their efficacy and their potential for abuse. The NeuPSIG provides a weak recommendation against the use of cannabinoids in NeP owing to potential for misuse, diversion, and long-term risks in susceptible individuals.[42] Side effects of cannabinoids can vary but usually include somnolence, "getting high," confusion, dizziness, tachycardia, and hypotension.[56]

Cannabinoid formulations in Canada currently consist of nabilone, nabiximols, and dried cannabis.[57] Dosing for dried cannabis is highly individualized and relies greatly on titration owing to complex pharmacology, interindividual genetic differences in cannabinoid receptors, metabolism, and previous exposure. In clinical trials with positive results using dried cannabis for NeP conditions, the delta-9-tetrahydrocannabinol dose per day did not exceed 125 mg, and maximum tetrahydrocannabinol by weight was 9.4%. Although there is no established dosing guideline for dried cannabis, the Health Canada monograph on cannabis provides "rough" dosing guidelines.[56] Dried cannabis is not approved or regulated by Health Canada because it has not gone through the necessary rigorous scientific trials for efficacy or safety. Provincial guides and policies on medical marijuana can be found on the Canadian Medical Protective Association website.[58] For family physicians starting, maintaining, or terminating dried cannabis prescriptions, preliminary guidelines have been created by the College of Family Physicians of Canada.[57]

As per current guidelines, cannabis is not appropriate to start in those who are younger than 25 years of age, might be pregnant, have cardiovascular disease, have a respiratory disease, have a history of psychosis, or have a substance use disorder. In patients naïve to cannabis, a trial with a synthetic cannabinoid, usually nabilone, should be considered first. If dried cannabis is prescribed, physicians must continue to follow up and monitor patients to assess for potential misuse, abuse, and efficacy. Discontinuation of cannabis therapy is warranted when there is clearly no benefit or it is causing harm to the patient.[57] It is important also to be cognizant of cannabis hyperemesis syndrome as a differential diagnosis in young patients who present with cyclic vomiting and compulsive hot bathing.[59] There are several large-scale Canadian initiatives under way with the aim of creating evidence-based recommendations on the prescription of medical cannabis.

Fourth-line analgesics. Selective serotonin reuptake inhibitors are another class of antidepressants that have some analgesic efficacy, with the exception of fluoxetine, in painful diabetic neuropathy and painful polyneuropathy.[60-63] Similar to SNRIs, there is a risk of serotonin syndrome with medications that increase serotonin levels and they are also contraindicated in combination with monoamine oxidase inhibitors.[64]

Topical lidocaine is a local anesthetic useful in the management of peripheral NeP. It remains a second-line agent specifically for postherpetic neuralgia.[18]

Table 3. Selected opioid safety considerations

OPIOID	SAFETY CONSIDERATION
Codeine	• In breastfeeding women, there is risk of morphine toxicity in infants owing to rapid conversion of codeine to morphine
Tramadol	• Associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin level (eg, SSRIs)
Morphine	• In patients with renal dysfunction, morphine-6-glucuronide, an active metabolite of morphine, can accumulate to toxic levels
Oxycodone, hydromorphone, hydrocodone	• As with all opioids, use with caution in patients at risk of opioid misuse and addiction
Fentanyl	• Before starting fentanyl, ensure the patient has been fully opioid tolerant during the previous 2 wk (total dose of at least 60-90 mg/d morphine equivalence) on a scheduled dose (at least twice daily for CR or 4 times daily for IR) • Do not switch from codeine to fentanyl regardless of the codeine dose, as some patients taking codeine might have little or no opioid tolerance • Maintain the starting dose for at least 6 d and use extra caution with patients at higher risk of overdose (eg, the elderly, those taking benzodiazepines) • Advise the patient as follows: -Be alert for signs of overdose; if detected, remove the patch and seek medical attention -Apply the patches as prescribed; do not apply more than 1 patch at a time -Avoid heat sources such as heating pads -Enforce patch-for-patch exchange at pharmacy to reduce diversion
Methadone	• Use methadone to treat pain only if you hold a written Health Canada exemption • Titration is hazardous because of its very long half-life, which leads to bioaccumulation
Meperidine	• Not recommended for use in CNCP owing to poor bioavailability and inferior effectiveness to codeine • Normeperidine, a metabolite of meperidine, can accumulate with frequent use causing seizures and delirium
Acetaminophen-opioid combinations	• Use with caution to not exceed maximum dose of 3.2 g/d of acetaminophen for adults (10 tablets/d of opioid-acetaminophen combinations) • No more than 8 tablets/d for tramadol-acetaminophen combinations • Warn alcohol drinkers to not mix alcohol with acetaminophen
CR formulations	• Each CR tablet can contain a higher opioid dose than IR formulations do and can be converted to IR by biting or crushing the tablet
Tapentadol	• Contraindicated in those with severe hepatic or renal dysfunction, or taking monoamine oxidase inhibitors • Small risk of seizure seen in postmarketing reports
Parenteral opioids	• Parenteral opioids are not recommended for treatment of CNCP owing to increased risk of overdose, abuse, addiction, and infection

CNCP—chronic noncancer pain, CR—controlled release, IR—immediate release, SSRI—selective serotonin reuptake inhibitor.
Adapted with permission from the Michael G. DeGroote National Pain Centre.[46]

However, there was no benefit shown in postsurgical nerve injury or in mixed NeP.[65,66] Topical lidocaine is safe, as only negligible levels are detected in blood and there are rarely any systemic side effects with topical use.[67]

Capsaicin is another topical agent with evidence for effectiveness at high concentrations (8%) in postherpetic neuralgia and in painful HIV neuropathy for up to 12 weeks after a single application.[68] As initial application of capsaicin causes sensitivity of nociceptors leading to an intense burning sensation, local anesthetic before application might be required. In Canada, the high-potency capsaicin patch may be obtained through compassionate release.

Methadone is a synthetic opioid with unique *N*-methyl-D-aspartate and SNRI properties.[69] Only small RCTs and surveys have suggested efficacy in mixed NeP conditions.[70-72] In Canada, a specialized methadone exemption is required for prescribing and guidelines are available for its management in chronic pain.[73]

Tapentadol is a newer opioid available in Canada with analgesic effect through μ-receptors and monoamine reuptake inhibition, but minimal effect on serotonin reuptake. This dual analgesic effect might contribute to its efficacy in treating painful diabetic neuropathy.[74] Like other opioids, common side effects include nausea and vomiting, somnolence, and dizziness but with lower incidence

compared with oxycodone. Another advantage is the lower potential for metabolic variation due to enzyme polymorphism. Similar to tramadol, serotonin syndrome can occur when combined with other serotonergic drugs but at a reduced rate.[75] As the efficacy of tapentadol has only been studied in a single NeP pain model, it is considered a fourth-line agent and is not included as a second-line treatment with tramadol and other opioids.

Other anticonvulsants studied in NeP management include lamotrigine, lacosamide, topiramate, and valproic acid. Lamotrigine provided negative results in studies of diabetic neuropathy, mixed NeP, chemotherapy-induced NeP, and spinal cord injury pain. Results of small studies investigating lamotrigine's effect in HIV neuropathy, trigeminal neuralgia, and central poststroke pain were positive.[76] Lacosamide has been mostly studied in the context of painful diabetic neuropathy with modest benefit.[77] Topiramate and valproic acid have had mixed results in NeP trials.[18]

Botulinum toxin injections represent a novel treatment in NeP with positive results in diabetic neuropathy and focal painful neuropathy. However, these studies are underpowered, with small sample sizes.[78,79] Therefore, the evidence for botulinum toxin remains preliminary and further evidence is needed.

Combination pharmacotherapy. Recent review of combination pharmacotherapy in the treatment of NeP has involved variations of an opioid with gabapentin, pregabalin, or a TCA, the combination of gabapentin and nortriptyline, and various topical medications.[80] A meta-analysis of the combination of gabapentin with an opioid showed superiority in terms of analgesia when compared with gabapentin alone, but the combination also led to more discontinuations owing to side effects.[80] An RCT comparing duloxetine (60 mg daily) and pregabalin (300 mg daily) to high-dose duloxetine or pregabalin monotherapy did not yield any difference in 24-hour pain; however, all secondary outcome measures favoured combination therapy.[81] Current evidence does not support a recommendation of any one specific drug combination for NeP, but it remains an important and understudied strategy.

Conclusion

Based on the 2014 CPS NeP consensus statement,[7] gabapentinoids and TCAs continue to play an important role for first-line management of NeP. As a result of evidence published since the 2007 CPS NeP consensus statement, SNRIs are now also among the first-line agents. Topical lidocaine, a previous second-line agent, remains in the same tier of treatment only for postherpetic neuralgia, but is otherwise now a fourth-line analgesic. Opioids including tramadol have been moved from third-line to second-line treatment. Cannabinoids (including dried cannabis) have been elevated from fourth-line agents to a third-line treatment option for chronic NeP. The fourth-line analgesic medications are understudied but can still be of therapeutic value when other options have failed or are intolerable.

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All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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None declared

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References

1. Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003;348(13):1279-81.
2. Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. *CMAJ* 2006;175(3):265-75.
3. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008;136(3):380-7. Epub 2007 Sep 20.
4. Torrance N, Smith BH, Watson MC, Bennett MI. Medication and treatment use in primary care patients with chronic pain of predominantly neuropathic origin. *Fam Pract* 2007;24(5):481-5. Epub 2007 Aug 1.
5. Kautio AL, Haanpää M, Kautiainen H, Kalso E, Saarto T. Burden of chemotherapy-induced neuropathy—a cross-sectional study. *Support Care Cancer* 2011;19(12):1991-6. Epub 2010 Nov 16.
6. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007;12(1):13-21.
7. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag* 2014;19(6):328-35.
8. Ashman EJ, Gronseth GS. Level of evidence reviews: three years of progress. *Neurology* 2012;79(1):13-4. Epub 2012 Jun 20.
9. Dworkin RH, Turk DC, Basch E, Berger A, Cleeland C, Farrar JT, et al. Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy. *Pain* 2011;152(8):1705-8. Epub 2011 Mar 10.
10. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain* 2005;6(3):149-58.
11. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005;114(1-2):29-36. Epub 2005 Jan 26.
12. Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID Pain. *Curr Med Res Opin* 2006;22(8):1555-65.
13. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011;152(1):14-27. Epub 2010 Sep 19.
14. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70(18):1630-5. Epub 2007 Nov 14.
15. Working Group on Curriculum Review. *CanMEDS—Family Medicine.* Mississauga, ON: College of Family Physicians of Canada; 2009. Available from: **www.cfpc.ca/uploadedFiles/Education/CanMeds%20FM%20Eng.pdf**. Accessed 2017 Sep 6.
16. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17(9):1113-e88. Epub 2010 Apr 9.
17. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM R* 2011;3(4):345-52, 352.e1-21.
18. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150(3):573-81.
19. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004;110(3): 697-706. Erratum in: *Pain* 2005;113(1-2):248.
20. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006;67(10):1792-800.
21. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008;136(1-2):150-7. Epub 2007 Aug 20.
22. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011;152(5):1018-23. Epub 2011 Feb 12.
23. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;118(3):289-305. Epub 2005 Oct 6.
24. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013;309(13):1359-67.
25. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007;110(9):2110-8.

26. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology* 2003;60(8):1284-9.
27. Zakrzewska JM. Medical management of trigeminal neuropathic pains. *Expert Opin Pharmacother* 2010;11(8):1239-54.
28. Jensen TS, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. *Curr Opin Neurol* 2009;22(5):467-74.
29. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68(2-3):217-27.
30. Sullivan MJ, Reesor K, Mikail S, Fisher R. The treatment of depression in chronic low back pain: review and recommendations. *Pain* 1992;50(1):5-13.
31. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132(3):237-51. Epub 2007 Oct 24.
32. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44(2):213-8. Epub 2014 Oct 16.
33. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63(11):2227-46. Epub 2015 Oct 8.
34. *Neurontin* [product monograph]. Kirkland, QC: Pfizer Canada Inc; 2014. Available from: **www.pfizer.ca/sites/g/files/g10023216/f/201505/NEURONTIN_PM_175273_EN_12September2014.pdf**. Accessed 2017 Sep 6.
35. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med* 2009;122(10 Suppl):S22-32.
36. Harada E, Tokuoka H, Fujikoshi S, Funai J, Wohlreich MM, Ossipov MH, et al. Is duloxetine's effect on painful physical symptoms in depression an indirect result of improvement of depressive symptoms? Pooled analyses of three randomized controlled trials. *Pain* 2016;157(3):577-84.
37. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. *J Pain Res* 2014;7:339-51.
38. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001;25(6):871-80.
39. Richelson E. Pharmacology of antidepressants. *Mayo Clin Proc* 2001;76(5):511-27.
40. Wright A, Luedtke KE, Vandenberg C. Duloxetine in the treatment of chronic pain due to fibromyalgia and diabetic neuropathy. *J Pain Res* 2010;4:1-10.
41. Barowsky J, Schwartz TL. An evidence-based approach to augmentation and combination strategies for: treatment-resistant depression. *Psychiatry* (Edgmont) 2006;3(7):42-61.
42. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14(2):162-73. Epub 2015 Jan 7.
43. Tramadol—a new oral analgesic. *Med Lett Drugs Ther* 1995;37(952):59-62.
44. Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N, et al. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg* 2004;187(4):521-7.
45. Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and non-enriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag* 2011;16(5):337-51.
46. Michael G. DeGroote National Pain Centre. *2017 Canadian guideline for opioids for chronic non-cancer pain*. Hamilton, ON: McMaster University; 2017. Available from: **http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf**. Accessed 2017 Oct 16.
47. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain* 2002;100(3):213-7.
48. Demarest SP, Gill RS, Adler RA. Opioid endocrinopathy. *Endocr Pract* 2015;21(2):190-8. Erratum in: *Endocr Pract* 2015;21(5):559.
49. Furlan A, Robidas A. *My opioid manager*. Toronto, ON: Toronto Rehabilitation Institute, University Health Network; 2015. Available from: **www.opioidmanager.com**. Accessed 2017 Sep 6.
50. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, et al. The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. *J Pain Res* 2015;8:695-702.
51. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol* 2015;10(2):293-301. Epub 2015 Mar 22.
52. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65(6):812-9.
53. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004;329(7460):253. Epub 2004 Jul 16.
54. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. Epub 2012 Aug 23.
55. Meng H, Hanlon JG, Katznelson R, Ghanekar A, McGilvray I, Clarke H. The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. *Can J Anaesth* 2016;63(3):307-10. Epub 2015 Oct 27.
56. Health Canada. *Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids*. Ottawa, ON: Health Canada; 2013. Available from: **https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf**. Accessed 2017 Sep 6..
57. College of Family Physicians of Canada. *Authorizing dried cannabis for chronic pain or anxiety. Preliminary guidance*. Mississauga, ON: College of Family Physicians of Canada; 2014.
58. Canadian Medical Protective Association. *Medical marijuana: considerations for Canadian doctors*. Ottawa, ON: Canadian Medical Protective Association; 2016. Available from: **www.cmpa-acpm.ca/en/advice-publications/browse-articles/2014/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors**. Accessed 2017 Sep 6.
59. Ruffle JK, Bajgoric S, Samra K, Chandrapalan S, Aziz Q, Farmer AD. Cannabinoid hyperemesis syndrome: an important differential diagnosis of persistent unexplained vomiting. *Eur J Gastroenterol Hepatol* 2015;27(12):1403-8.
60. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326(19):1250-6.
61. Otto M, Bach FW, Jensen TS, Brøsen K, Sindrup SH. Escitalopram in painful polyneuropathy: a randomized, placebo-controlled, cross-over trial. *Pain* 2008;139(2):275-83. Epub 2008 Jun 10.
62. Sindrup SH, Bjerre U, Dejgaard A, Brøsen K, Aaes-Jørgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52(5):547-52.
63. Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42(2):135-44.
64. Sproule BA, Naranjo CA, Brenmer KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions. A critical review of the evidence. *Clin Pharmacokinet* 1997;33(6):454-71.
65. Cheville AL, Sloan JA, Northfelt DW, Jillella AP, Wong GY, Bearden JD 3rd, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). *Support Care Cancer* 2009;17(4):451-60. Epub 2009 Jan 13.
66. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. *Clin J Pain* 2008;24(1):51-5.
67. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother* 2002;36(2):236-40.
68. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2013;(2):CD007393.
69. Peng PW, Tumber PS, Gourlay D. Perioperative pain management of patients on methadone therapy. *Can J Anaesth* 2005;52(5):513-23.
70. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. *Pain Res Manag* 2003;8(3):149-54.
71. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliat Med* 2003;17(7):576-87.
72. Moulin DE, Palma D, Watling C, Schulz V. Methadone in the management of intractable neuropathic noncancer pain. *Can J Neurol Sci* 2005;32(3):340-3.
73. Lynch ME. A review of the use of methadone for the treatment of chronic noncancer pain. *Pain Res Manag* 2005;10(3):133-44.
74. Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011;27(1):151-62.
75. Vadivelu N, Timchenko A, Huang Y, Sinatra R. Tapentadol extended-release for treatment of chronic pain: a review. *J Pain Res* 2011;4:211-8. Epub 2011 Aug 1.
76. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev* 2011;(2):CD006044.
77. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(2):CD009318.
78. Lakhan SE, Velasco DN, Tepper D. Botulinum toxin-A for painful diabetic neuropathy: a meta-analysis. *Pain Med* 2015;16(9):1773-80. Epub 2015 Mar 20.
79. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol* 2008;64(3):274-83. Erratum in: *Ann Neurol* 2009;65(3):359.
80. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012;(7):CD008943.
81. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013;154(12):2616-25. Epub 2013 May 31.

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A Multicriteria Decision Analysis Comparing Pharmacotherapy for Chronic Neuropathic Pain, Including Cannabinoids and Cannabis-Based Medical Products

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Abstract

Background: Pharmacological management of chronic neuropathic pain (CNP) still represents a major clinical challenge. Collective harnessing of both the scientific evidence base and clinical experience (of clinicians and patients) can play a key role in informing treatment pathways and contribute to the debate on specific treatments (e.g., cannabinoids). A group of expert clinicians (pain specialists and psychiatrists), scientists, and patient representatives convened to assess the relative benefit–safety balance of 12 pharmacological treatments, including orally administered cannabinoids/cannabis-based medicinal products, for the treatment of CNP in adults.

Methods: A decision conference provided the process of creating a multicriteria decision analysis (MCDA) model, in which the group collectively scored the drugs on 17 effect criteria relevant to benefits and safety and then weighted the criteria for their clinical relevance.

Findings: Cannabis-based medicinal products consisting of tetrahydrocannabinol/cannabidiol (THC/CBD), in a 1:1 ratio, achieved the highest overall score, 79 (out of 100), followed by CBD dominant at 75, then THC dominant at 72. Duloxetine and the gabapentinoids scored in the 60s, amitriptyline, tramadol, and ibuprofen in the 50s, methadone and oxycodone in the 40s, and morphine and fentanyl in the 30s. Sensitivity analyses showed that even if the pain reduction and quality-of-life scores for THC/CBD and THC are halved, their benefit–safety balances remain better than those of the noncannabinoid drugs.

Interpretation: The benefit–safety profiles for cannabinoids were higher than for other commonly used medications for CNP largely because they contribute more to quality of life and have a more favorable side effect profile. The results also reflect the shortcomings of alternative pharmacological treatments with respect to safety and mitigation of neuropathic pain symptoms. Further high-quality clinical trials and systematic comprehensive

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Correction added on April 1, 2021 after first online publication of March 17, 2021: The article reflects Open Access, with copyright transferring to the author(s), and a Creative Commons Attribution Noncommercial License (CC-BY-NC) added (http://creativecommons.org/licenses/by-nc/4.0/).

capture of clinical experience with cannabinoids is warranted. These results demonstrate once again the complexity and multimodal mechanisms underlying the clinical experience and impact of chronic pain.

Keywords: neuropathic pain; analgesics; cannabis-based medical products; CBMP; multicriteria decision analysis; MCDA

Introduction

Cannabis-based medical products (CBMPs) are now approved in >20 countries and so accessible to hundreds of millions of patients.[1,2] But in some countries, notably the United Kingdom, there is very limited prescribing.[1,2] Reasons for this are varied and complex, including considerable medicolegal and bureaucratic hurdles,[2,3] but they also reflect a concern by the medical profession that the randomized control trial (RCT) evidence base for medical cannabis is limited and, for many of its possible indications, inconclusive. This attitude is opposite to that of many patient testimonies (both in the United Kingdom and in other countries) where medical cannabis is seen as an important addition to their treatment (UPA 2018). Similarly, clinicians with considerable practical experience with use of cannabis, including for pain management, also see this as an important and major addition to their armamentarium.[4,5] The Centre for Medical Cannabis (CMC) estimates that in the United Kingdom more than one million patients are using cannabis,[6] and almost all of them are obtaining it illegally, which presents them with significant legal and product quality risks.[2] Moreover, these patients are less likely to involve their health care specialist in the process and, therefore, manage their own treatment unsupervised.

Surveys highlight that pain is one of the conditions patients most commonly treated with medical cannabis[6,7] and a review by the National Academies of Sciences, Engineering, and Medicine (NASEM) in 2017 found the evidence base for chronic pain to be "substantial."[8] However, conclusions of recent meta-analyses and systematic reviews on the use of cannabinoids, cannabis and cannabis-based medicines to treat chronic neuropathic pain (CNP) have ranged from weakly positive to inconclusive or negative.[9–15] These differing conclusions may be the result of including different trial designs, different standards to evaluate the quality of evidence, and different weighting of the outcomes of efficacy, tolerability, and safety.[16,17] Thus, systematic reviews examining the same studies often arrived at different conclusions and recommendations.[18] The scientific literature examining the efficacy of cannabinoids, cannabis, and cannabis-based medicines for CNP is, therefore, still developing. An expert Task Force of the European Pain Federation recently published a position article that concluded that the quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for CNP. For all other chronic pain conditions (cancer, non-neuropathic noncancer pain), the use of cannabis-based medicines should be regarded as an individual therapeutic trial.[19] Recent RCTs examining the efficacy of cannabinoids, cannabis, and cannabis-based medicines for CNP are shown in Appendix Table A1. This study focuses exclusively on this area to narrow down the complexity of chronic pain.

Available data to date suggest that the use of cannabinoids for chronic pain is relatively safe, with little evidence for the increase of risk for experiencing serious adverse events, although nonserious adverse events may be common in the short-term period after use.[20,21] Notably, despite the rapidly increasing multitude of patients, there has never been an overdose fatality directly attributed to cannabis use reported in medical literature. As many patients with chronic pain often suffer from multiple comorbidities and physical disability, and considering the numerous safety concerns of current pain pharmacotherapy,[22–24] careful consideration of the safety profile is of crucial importance and improved harms assessment and reporting are needed in cannabinoid pain trials.[25]

This study was designed to explore the evidence base for the clinical utility of orally administered CBMPs (including cannabis extracts and cannabis-based medicines such as nabiximols [Sativex® is approved in 30 countries but not marketed in each] dronabinol, and nabilone) for management of CNP in adults by creating a multicriteria decision analysis (MCDA) model that compares these cannabinoid formulations with other drugs. The results of this modeling can provide prescribers and others with an updated viewpoint incorporating the current state of scientific knowledge as well as the cumulative clinical experience regarding the use of orally administered CBMPs for CNP in adults.

MCDA models about drugs often compare a single drug, or one drug at different doses, with a placebo as an approach for determining the extent to which

benefits exceed risks.[26,27] A recent trend is to compare one drug(s) to other drugs for the same medical condition.[28,29] The rationale for this is that drugs for a given medical condition differ in their benefit–safety profiles, so making those profiles explicit and quantitative, and balancing them using a collective expert decision process coupled with sensitivity analyses, can reveal new insights and provide information for guiding prescribers, policy makers and patients to complement and augment that available from RCT data. The MCDA process is particularly pertinent to areas such as CBMPs for CNP, where, due to the psychoactivity of cannabis, it is challenging to achieve true blinding in RCTs, and where the real-world use of CBMPs has continued to advance rapidly and controversially, despite a limited and relatively low-quality RCT evidence base. The issue of blinding has been specifically addressed with nabiximols with positive assessment of its validity due to flavoring and low dosing avoiding overt psychoactive adverse events.[30]

Methods

Experts ranging from pain clinicians with and without prescribing expertise in CBMPs from the United Kingdom, Denmark, Israel, and Germany, psychiatrists, a neurologist, researchers with expertise in cannabinoid pharmacology, decision analysis, and patient representatives with personal experience of CBMPs (representing the United Patients Alliance) were selected and invited to take part in the MCDA modeling process. The meeting was facilitated by L.D.P. with support from D.J.N., but neither of them participated in the scoring. Participants did not benefit financially from participating in the MCDA.

A subgroup met on December 9, 2019 to begin the process of developing the MCDA model, which would enable participants in the subsequent (January 2020) decision conference to complete their work in 1 day. The subgroup suggested that the medical condition should be chronic pain and they developed a list of drugs, including CBMPs, used to treat chronic pain. They also identified favorable and unfavorable effects of all treatments and suggested definitions of all these effects. This preliminary overview of an MCDA model's structure was sent to all participants before the decision conference.

A decision conference is a facilitated workshop[31] designed to resolve one or more issues of concern by building a quantitative model that incorporates the differing perspectives of the participants along with data and judgments about the relevance of the data to those issues of concern.[32] At the decision conference, participants agreed that the potential for orally administered cannabis-based medicinal products to treat CNP lasting >3 months in adults, rather than the broader "chronic pain" definition, was a key issue largely because there is more published evidence for cannabis-based medicinal products alone or in comparison with other approved medicines for CNP than that exists for other pain syndromes.

The process of extending and developing the model at the decision conference followed the steps developed during the 2009–2011 Benefit–Risk Project sponsored by the European Medicines Agency (EMA)[33] and by the 2009–2013 IMI-PROTECT administered by the EMA.[34] The steps are fully described in Chapter 5 of Benefit–Risk Assessment in Pharmaceutical Research and Development,[35] and follow the subheadings hereunder.

Effects and their definitions

At the decision conference, participants reviewed the subgroup's benefits and safety effects of medical treatments for CNP. They agreed that pain relief and quality of life were the two benefits, and they added seven more safety effects. These are shown in the Effects Tree of Figure 1, which was created using Hiview3 software,[36] with agreed definitions in Table 1.

Treatment options

The group considered 12 pharmacotherapies that are widely used in chronic pain syndromes. Three different types of CBMPs were distinguished: 1:1 ratio Δ^9—tetrahydrocannabinol (THC): cannabidiol (CBD) products (e.g., Sativex or 1:1 THC:CBD extracts), CBD-dominant products (either purified CBD or a CBD-rich extract with very low or no THC) and THC-dominant products (either purified THC or a THC-rich extract with i.e., with very low or no CBD), administered orally or by sublingual routes. We chose to consider orally administered pharmacotherapies only, and not to include inhalation therapies (although the most commonly used) because of expert recommendations against smoking[19] and health concerns relating to other methods of inhalation.

1	THC/CBD 1:1	7	Tramadol
2	CBD dominant	8	Ibuprofen
3	THC dominant	9	Methadone
4	Duloxetine	10	Oxycodone
5	Gabapentinoids	11	Morphine
6	Amitriptyline	12	Fentanyl

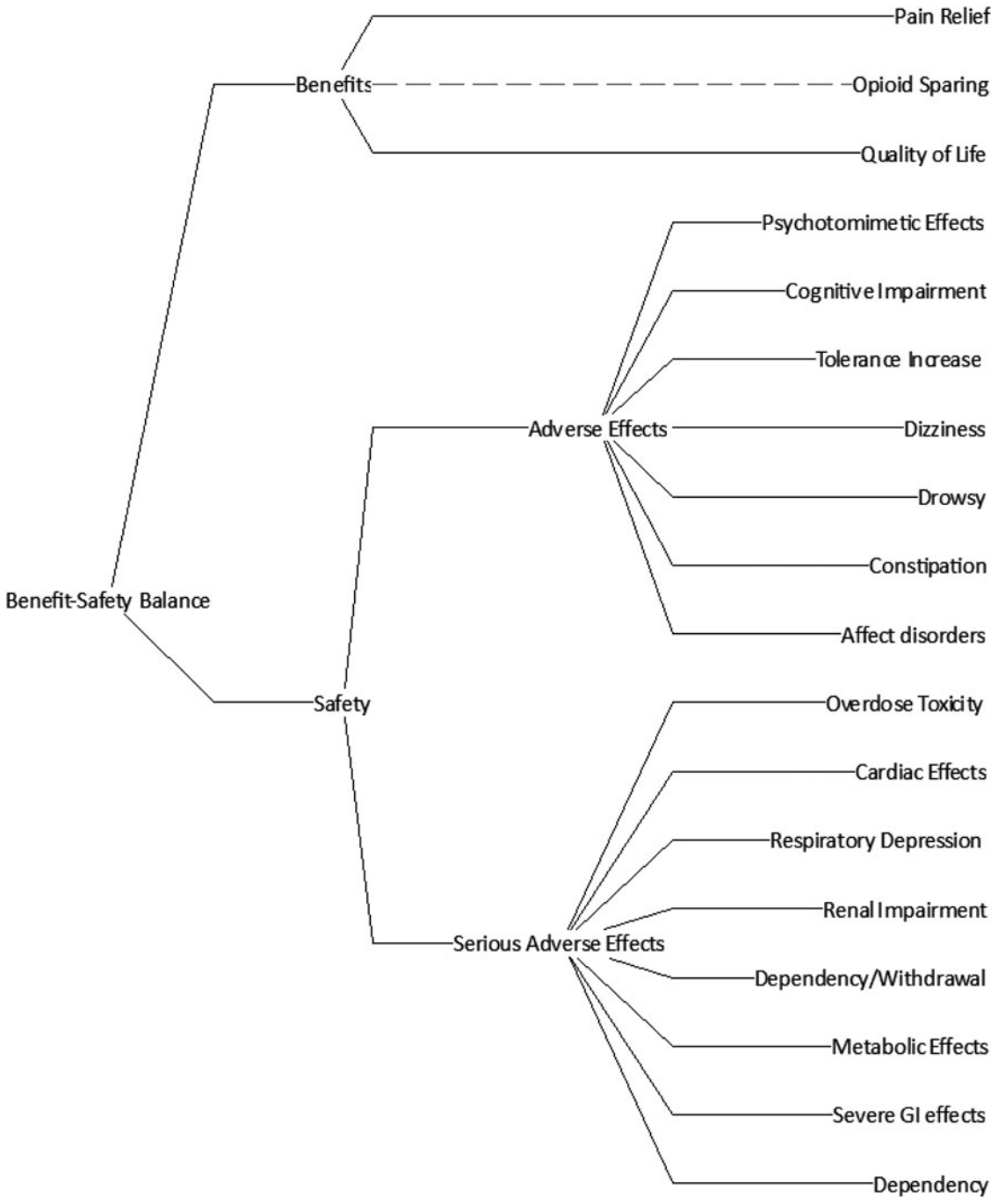

FIG. 1. The Effects Tree for assessing the relative benefit–safety of neuropathic pain pharmacotherapy.

Scoring the drugs on the criteria

Participants evaluated the pharmacotherapies relative to each other on 0–100 scales, one scale for each effect criterion, similar to the one for pain relief shown in Figure 2. First, the group agreed which options were most preferred for their clinical value, and these were assigned an arbitrary score of 100. Second, they agreed the least preferred and assigned it a score of zero. Third, the group discussed, debated, and agreed scores between 0 and 100 for the remaining options. All

Table 1. Definitions of the Favorable and Unfavorable Effects

	Effect	Description
Favorable effects	Pain relief	Proportion of patients reporting >30% reduction in neuropathic pain relief compared with baseline
	Opioid sparing	Meaningful reduction in milligrams of 24-h morphine consumption
	Quality of life	Improvement in quality-of-life score
Unfavorable effects Adverse events	Psychotomimetic	Proportion of patients experiencing psychotomimetic effects
	Cognitive impairment	Proportion of patients experiencing cognitive impairment
	Tolerance increase	Proportion of patients requiring more drug as tolerance increases
	Dizziness	Proportion of patients experiencing dizziness
	Drowsy	Proportion of patients experiencing drowsiness
	Constipation	Proportion of patients experiencing constipation
	Affect disorders	Proportion of patients experiencing affect disorders. Includes anxiety, depression, emotional blunting, decreased motivation, and disconnect
Unfavorable effects Serious adverse events	Overdose toxicity	The potential for toxic effects from accidental of deliberate overdosing
	Cardiac effects	Proportion of patients experiencing cardiac effect
	Respiratory depression	Proportion of patients experiencing respiratory depression
	Renal impairment	Proportion of patients experiencing renal impairments
	Withdrawal	Proportion of patients experiencing drug withdrawal *per se*
	Metabolic effects	Proportion of patients experiencing metabolic effects. Includes hypoglycemic effects, diabetics, weight changes, libido, and osteoporosis.
	Gastrointestinal	Proportion of patients experiencing gastrointestinal effects. Includes bleeds and ulcers.
	Dependency	The likelihood of increasing the dosage

numbers represent the judged strength of preference for the pharmacotherapies; higher numbers representing more effectiveness for the favorable effects, and better safety for the unfavorable effects.

The properties of these 0–100 scales are similar to those of a Celsius scale, whose 0 and 100 points are based on the freezing and boiling points of water at sea level. Zero does not represent no temperature and 100 is not a maximum temperature; the zero for ibuprofen simply means it has the least effect on pain control, whereas the three pharmacotherapies at 100 are tied for having the best effect.

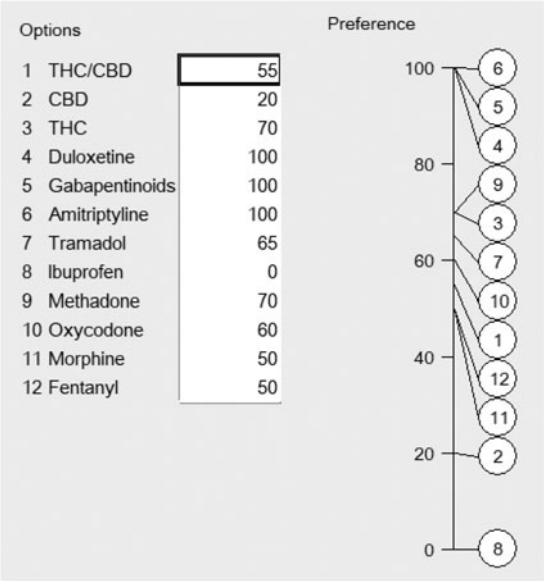

FIG. 2. Scores agreed by participants for pain relief.

In scoring the options, participants were given a few moments to think of an appropriate number, compared with the zero and 100, then to say what they thought, followed by group discussion. This "think, reveal, discuss" process was intended to prevent participants from anchoring on the first person to suggest a number in open discussion,[37] an approach that minimizes bias in group assessments.

Consistency checks initiated by the facilitator were intended to ensure the internal consistency in the preference values assessed by the group. For example, the facilitator asked, "Morphine has been scored at 50, duloxetine at 100 and ibuprofen at 0 for pain relief. Is duloxetine really as much better than morphine as ibuprofen is worse?" This sort of question helps assessors to provide realistic numbers. It also avoids interpreting ratios of numbers. Duloxetine is not twice better than morphine for pain relief because ibuprofen can provide some pain relief to some patients, so its zero is merely defining a point on a relative scale, similar to zero degrees in Celsius temperature (Table 2).

Weighting the effect criteria

The scoring process resulted in 17 0–100 scales, one for each effect criterion, but it is evident that not all scales represent the same ranges of added clinical value, so

Table 2. Input Preference Scores for Each of the Benefit and Safety Effects

	Weight	THC/CBD	CBD	THC	Duloxetine	Gabapentinoids	Amitriptyline	Tramadol	Ibuprofen	Methadone	Oxycodone	Morphine	Fentanyl
Pain relief	14.5	55	20	70	100	100	100	65	0	70	60	50	50
Opioid sparing	0	80	30	100	30	70	40	20	0	50	0	0	0
Quality of life	20.7	100	40	100	40	50	40	30	0	40	30	20	20
Psychotomimetic	5.1	50	100	0	100	100	100	100	100	100	100	100	100
Cognitive impairment	5.7	70	100	55	20	0	0	50	100	50	20	20	20
Tolerance	2.5	65	100	50	90	45	80	40	100	70	20	20	0
Dizziness	4.9	40	90	20	30	0	0	20	100	30	20	20	20
Drowsy	3.4	50	80	35	40	10	0	60	100	50	20	20	20
Constipation	3.4	100	100	100	90	90	75	40	100	10	10	0	20
Affect disorders	4.6	85	100	70	40	50	40	25	100	0	0	0	0
Overdose toxicity	8.4	100	100	90	60	70	20	40	60	10	20	20	0
Cardiac effects	5	70	100	40	40	90	0	70	80	40	80	80	80
Respiratory depress	6.3	100	100	100	90	60	80	60	100	30	20	20	0
Renal impairment	4.4	100	100	100	100	100	100	100	0	100	100	100	100
Withdrawal	1.5	50	100	20	10	0	30	40	80	0	10	10	0
Metabolic effects	2.5	75	90	50	75	10	50	75	100	0	0	0	0
Severe GI effects	4.4	100	100	100	100	100	100	90	0	100	100	100	100
Dependency	2.5	75	100	50	50	0	50	0	100	0	0	0	0

CBD, cannabidiol; GI, gastrointestinal; THC, tetrahydrocannabinol.

participants in the decision conference assigned weights to each. These are scale constants that equate the units of preference value across the scales. This weighting process is analogous to recognizing that both Fahrenheit and Celsius scales contain 0–100 portions, but the swing in temperature on the Celsius scale is a greater range of temperature: it takes 9 Fahrenheit degrees to equal 5 Celsius degrees, a ratio of 9:5.

In MCDA, the process is called "swing weighting" because it compares the swing from least to most preferred positions on one scale compared with another.[38] It is not just the importance of the effect, rather it represents both the objective difference between least and most preferred positions on a scale, and how much the assessors care about that difference, which usually means judging the clinical relevance of the difference. The weighting process went through three stages: (1) relative weighting of the criteria for the benefit effects, (2) relative weighting comparing swings for the adverse safety effects, then for the serious adverse effects, and (3) relative weighting of the highest-weighted benefit effect against the highest-weighted safety effect.

The weighting process in MCDA preserves the ratios of all weights even though they are eventually normalized to ensure they sum to 1.00 (displayed in this report as 100) across all the criteria before multiplying by the scores to give the final weighted preference values. The group judged the clinical difference between the best and worst drug for quality of life to be the largest difference for this set of drugs, with pain relief the second largest best–worst difference.

Results

Multiplying preference values by the corresponding swing weights and summing those products for each drug gives the overall weighted preference values shown in Table 3. The figures in the white rows are now referred to as benefits and safety because they represent the weighted input evaluations separately for the two benefits and the 15 safety effects. The bottom total row shows the weighted average of the two weighted sums in each column, providing a single figure that represents each drug's benefit–risk balance. For example, the equation for THC/CBD is simply $(81 \times 0.352) + (78 \times 0.648) = 79$. Figure 3 shows bar graphs of the separate weighted benefits and safety.

The breakdown of the weighted benefit and risks is shown in Figure 4, with a separate color associated with each of the 17 effect criteria. The figure is based on the weighted preference values shown in Table 4.

Table 3. Weighted Benefits and Safety, and Their Weighted Totals

Effect	Weight	THC/CBD	CBD	THC	Duloxetine	Gabapentinoids	Amitriptyline	Tramadol	Ibuprofen	Methadone	Oxycodone	Morphine	Fentanyl
Benefits	35.2	81	32	88	65	71	65	44	0	52	42	32	32
Safety	64.8	78	98	63	63	54	46	56	79	41	38	37	33
Total	100	79	75	72	64	60	53	52	51	45	40	36	33

This final table, called an Effects Table, provides the information for comparing the effects for any of the drugs as the weighting process has provided a common unit of preference value. Recall that only differences between the weighted preference values and/or their totals can be compared meaningfully, not their ratios.

Trade-offs between benefits and safety

At this point it would be useful to see the separate weighted preference values for the benefits and for the safety effects without regard for the trade-off weight between those two nodes. This is shown in Figure 5. The circles are located at the values of benefits and safety from the corresponding rows of Table 3.

The ideal position on this graph would be the upper right, a beneficial safe pharmacotherapy, scoring 100 and 100, but there is no drug that is best in overall benefits and safety. THC/CBD is the best compromise between the higher benefits but less safety of THC, on the one hand, or the safer but lesser benefits of CBD, on the other hand.

Those three drugs define what is known as the "efficient frontier;" there is no better drug outside the blue shading. However, close examination reveals a unique feature: THC/CBD and THC are better in benefits and safety than all the noncannabinoid pharmacotherapies. The only exception is ibuprofen, whose safety score is 79 compared with 78 for THC/CBD. For all the other noncannabinoids, at least one of the three CBMPs is better. If a regression line were fit through the noncannabinoids, excepting ibuprofen, it would be tilted from lower left to upper right, which shows a trend for delivering more benefit at greater safety, an interesting feature.

Sensitivity analyses

Some participants were surprised to see the CBMPs dominating the other drugs and requested that sensitivity analyses be performed to address any potential bias (or perceived bias) in the group's scores and weights. These sensitivity analyses involved making changes to the inputs, both during and after the decision conference, to demonstrate the extent to which results would change with different scores or weights.

Changes in the weights were explored for all the effect criteria and the nodes in the Effect Tree. Nearly all showed that the dominance of the CBMPs remained, although not necessarily as strongly, over plausible ranges for weights. The only effect that breaks the dominance is shown in Figure 6.

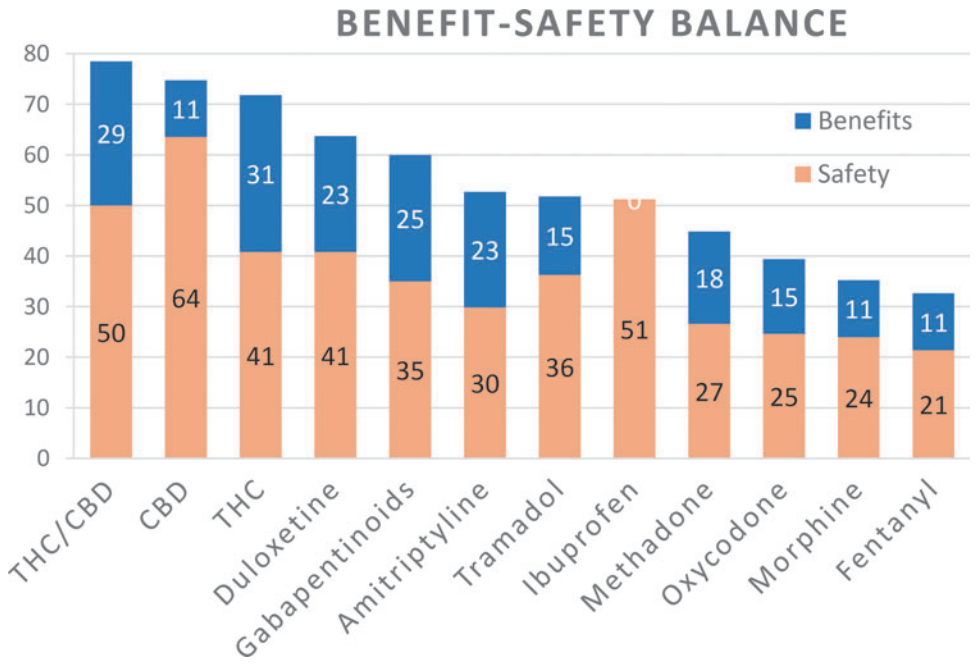

FIG. 3. The overall weighted preference values for the neuropathic pain pharmacotherapies. More blue means more benefit, more red indicates more safety.

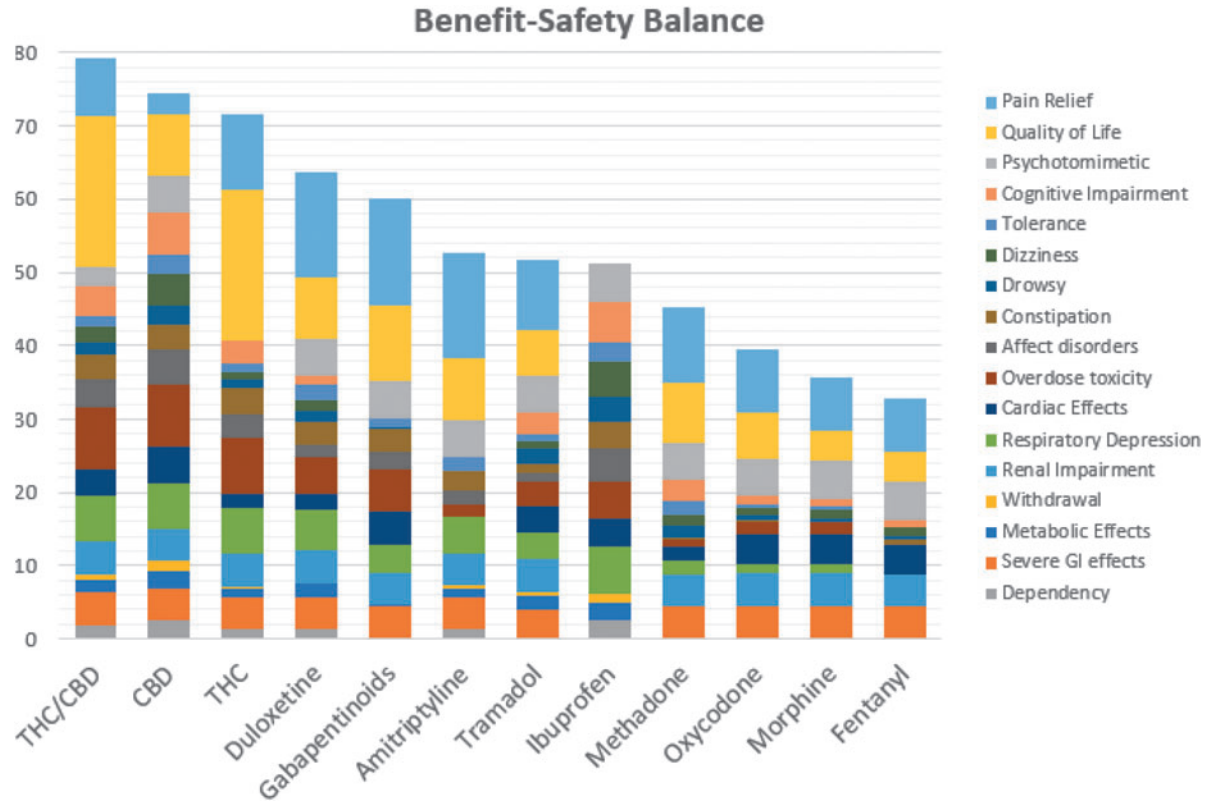

FIG. 4. Contributions to the totals by each of the 17 effects. The top blue (pain relief) and yellow (quality of life) sections of each bar show the magnitude of benefits; the rest show safety.

Table 4. Effects Table of Weighted Preference Values

Effects	Weight	THC/CBD	CBD	THC	Duloxetine	Gabapentinoids	Amitriptyline	Tramadol	Ibuprofen	Methadone	Oxycodone	Morphine	Fentanyl
Benefits													
Pain relief	14.5	8.0	2.9	10.2	**14.5**	**14.5**	**14.5**	9.4	0.0	10.2	8.7	7.3	7.3
Quality of life	20.7	**20.7**	8.3	**20.7**	8.3	10.4	8.3	6.2	0.0	8.3	6.2	4.1	4.1
Safety—AEs													
Psychotomimetic	5.1	2.6	5.1	**0**	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1	5.1
Cognitive Impairment	5.7	4.0	5.7	3.1	1.1	**0**	**0**	2.9	5.7	2.9	1.1	1.1	1.1
Tolerance	2.5	1.6	2.5	1.3	2.3	1.1	2.0	1.0	2.5	1.8	0.5	0.5	**0**
Dizziness	4.9	2.0	4.4	1.0	1.5	**0**	**0**	1.0	4.9	1.5	1.0	1.0	1.0
Drowsy	3.4	1.7	2.7	1.2	1.4	0.3	**0**	2.0	3.4	1.7	0.7	0.7	0.7
Constipation	3.4	3.4	3.4	3.4	3.1	3.1	2.6	1.4	3.4	0.3	0.3	**0**	0.7
Affect disorders	4.6	3.9	4.6	3.2	1.8	2.3	1.8	1.2	4.6	**0**	**0**	**0**	**0**
Safety—SAEs													
Overdose toxicity	8.4	8.4	8.4	7.6	5.0	5.9	1.7	3.4	5.0	0.8	1.7	1.7	**0**
Cardiac effects	5.0	3.5	5.0	2.0	2.0	4.5	**0**	3.5	4.0	2.0	4.0	4.0	4.0
Respiratory depress	6.3	6.3	6.3	6.3	5.7	3.8	5.0	3.8	6.3	1.9	1.3	1.3	**0**
Renal impairment	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	**0**	4.4	4.4	4.4	4.4
Withdrawal	1.5	0.8	1.5	0.3	0.2	**0**	0.5	0.6	1.2	**0**	0.2	0.2	**0**
Metabolic effects	2.5	1.9	2.3	1.3	1.9	0.3	1.3	1.9	2.5	**0**	**0**	**0**	**0**
Severe GI effects	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.0	**0**	4.4	4.4	4.4	4.4
Dependency	2.5	1.9	2.5	1.3	1.3	**0**	1.3	**0**	2.5	**0**	**0**	**0**	**0**

Boldface values identify best benefit and worst safety.

The vertical red line is located at the current weight for pain relief, 14.5 (from Fig. 3). All the other lines represent their total score as the weight on pain relief is changed. The intersection of the vertical red line with each of the other lines occurs at their total values shown in Table 3. As the weight is increased, THC/CBD declines in preference, with duloxetine emerging as better when the weight exceeds 35, followed closely by the gabapentinoids and amitriptyline, then opioids.

After the decision conference, one participant suggested we had scored THC/CBD and THC too high on pain relief and quality of life and suggested those two scores be decreased by half. The result is shown in the benefit versus safety plot of Figure 7.

Halving just the pain control scores shows that THC/CBD and THC still dominate the pharmacotherapies, but less so than shown in Figure 5. In addition, if the quality-of-life scores for the two cannabinoids are halved, the right plot shows that duloxetine and the gabapentinoids move up to the efficient frontier, with amitriptyline slightly less good.

Differences

The aforementioned plots made no assumption about the trade-off between benefits and safety. Taking account of that trade-off makes it possible to compare the performance between pharmacotherapies because the scores are based on a common unit of preference value. The aforementioned analyses show that decisions about the drug will be different depending on whether a patient or clinician is more concerned about pain relief or about quality of life, as seen most clearly in Figure 8.

The weighted difference (Wtd Diff) column shows the result of multiplying the cumulative weight (Cum Wt) for each effect by the difference in preference values (Diff) between the two drugs shown in the top white fields. The effects have been put in order of the Wtd Diffs of the pair of pharmacotherapies, with the Wtd Diff sum equal to the difference in their overall preference values (negative signs favor the right-listed pharmacotherapies over the left one). The green horizontal bar graphs show the relative advantages of THC:CBD, and the red bars are the advantages of duloxetine. The sums of those positive and negative weighted scores equals the 15-point difference in their total scores shown in Table 3.

Discussion

This is the first time that CBMPs have been subjected to an MCDA and compared with each other and against other neuropathic pain medications, based on

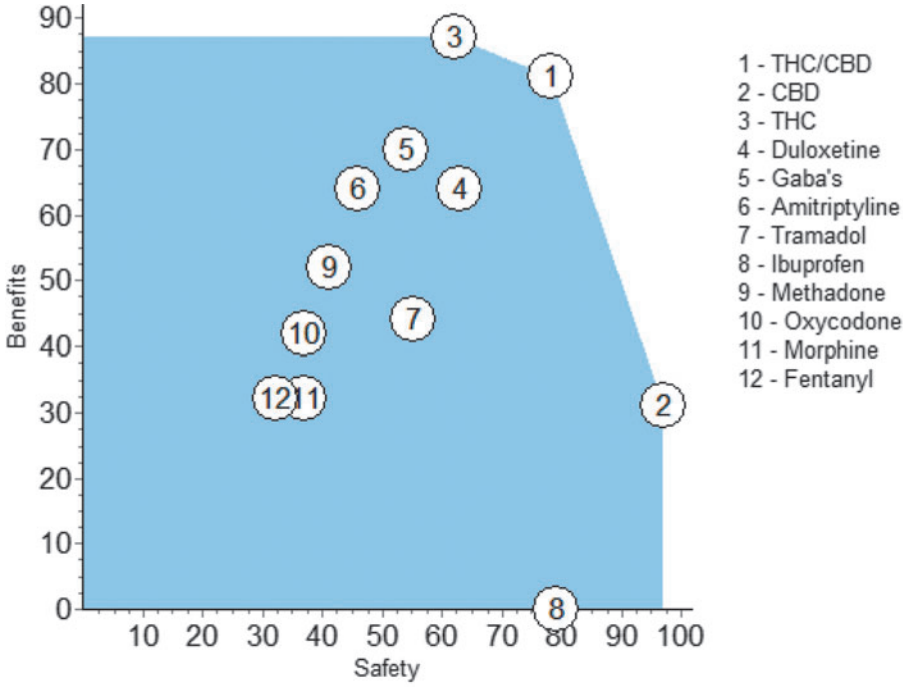

FIG. 5. Benefit preference values versus the safety preference values shown in Table 3.

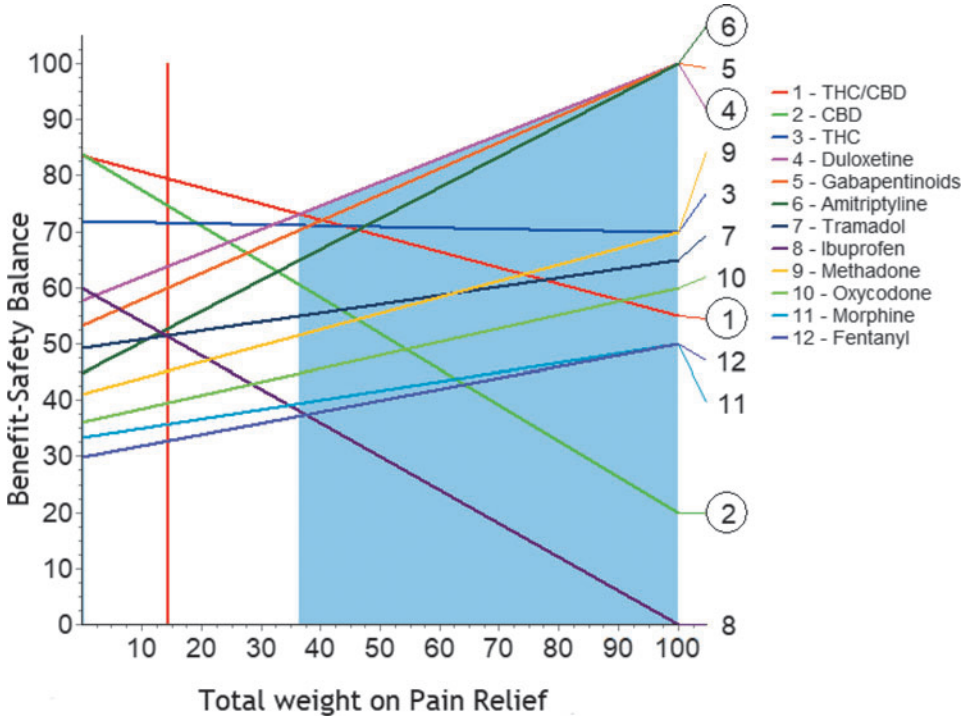

FIG. 6. Sensitivity analysis for pain relief.

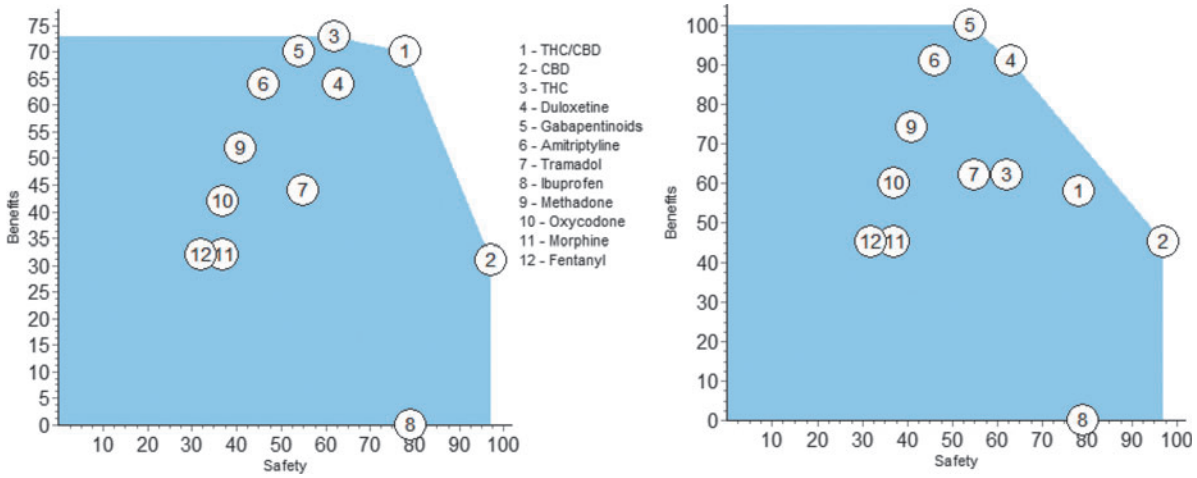

FIG. 7. The results of sensitivity analyses on the input preference scores for THC/CBD and THC. Halving the Pain Control scores gives the left plot. An additional halving of the quality-of-life scores is shown in the right plot. CBD, cannabidiol; THC, tetrahydrocannabinol.

Compare THC/CBD minus Duloxetine

	Model Order	Cum Wt	Diff	Wtd Diff	Sum
Benefits	Quality of Life	20.7	60	12.4	12.4
Serious Adverse Effe	Overdose toxicity	8.4	40	3.4	15.8
Adverse Effects	Cognitive Impairment	5.7	50	2.9	18.7
Adverse Effects	Affect disorders	4.6	45	2.1	20.8
Serious Adverse Effe	Cardiac	5.0	30	1.5	22.3
Serious Adverse Effe	Dependency	2.5	25	0.6	22.9
Serious Adverse Effe	Respiratory Depress	6.3	10	0.6	23.5
Serious Adverse Effe	Withdrawal	1.5	40	0.6	24.1
Adverse Effects	Dizziness	4.9	10	0.5	24.6
Adverse Effects	Drowsy	3.4	10	0.3	25.0
Adverse Effects	Constipation	3.4	10	0.3	25.3
Benefits	Opioid Sparing	0.0	50	0.0	25.3
Serious Adverse Effe	Renal Impairment	4.4	0	0.0	25.3
Serious Adverse Effe	Metabolic Effects	2.5	0	0.0	25.3
Serious Adverse Effe	Severe GI effects	4.4	0	0.0	25.3
Adverse Effects	Tolerance	2.5	-25	-0.6	24.7
Adverse Effects	Psychotomimetic	5.1	-50	-2.5	22.1
Benefits	Pain Relief	14.5	-45	-6.5	15.6
		100.0		15.6	

FIG. 8. THC/CBD is better for quality of life, but duloxetine is better for pain relief. This pattern is similar for gabapentinoids and amitriptyline as comparators with THC/CBD.

benefit–safety balances. In this study, we compared three cannabinoid options and nine noncannabinoid medications for their beneficial effects on pain relief and quality of life, against seven adverse effects, and eight serious adverse effects. The results showed the best benefit–safety balance, 79, for THC/CBD (1:1), and least good balance for fentanyl, 33. The 46-point difference in performance is substantial, with about two-thirds of the difference contributed by better quality of life and lack of overdose toxicity and respiratory depression.

The dominance analysis showed that two CBMPs options, THC/CBD and THC, are more beneficial and safer than any of the alternatives. However, that generalization is only valid at the level of the combined benefits and combined safety effects. The Effects Table at Figure 4 gives the weighted preference values for all 204 combinations of the 12 pharmacotherapies and 17 effects. The table shows duloxetine, gabapentinoids, and amitriptyline as best for pain relief, with THC/CBD and THC as best for quality of life. The Effects Table also highlights the worst side effect for each drug. Only THC/CBD, CBD, and duloxetine avoid worst scores for side effects, whereas THC has only one worst score, for psychotomimetic effects.

Sensitivity analyses—conducted jointly during the MCDA process—helped to resolve uncertainty about the data, such as it is, and disagreements about weights. Fortunately, MCDA models are fairly robust to imprecision in the inputs,[39] which was borne out for this MCDA on CBMPs The benefit versus safety graphs showed that THC/CBD remained the most preferred pharmacotherapy over wide ranges of weights on the safety node and the individual effects. Since this emerged from a multitude of questions and comparisons, rather than straightforward simple scoring, the final dominance at the benefit–safety level of the cannabinoids over all the other medicines was initially surprising to the group. However, this became reasonable and accepted by the group in light of the recognition that CBMPs scores were driven by their beneficial effects on quality of life, combined with their superior side effects profile. The 15-point superiority of THC/CBD over duloxetine, for example, was due to better quality of life, less overdose toxicity, cognitive impairment, and less disturbance on affect, which provided a net benefit for the CBMPs over duloxetine's better pain relief and psychotomimetic effects. This profile was similar to the difference between THC/CBD and gabapentinoids and amitriptyline.

Many pain patients seek medical attention precisely because their pain interferes with some or all aspects of their quality of life.[40] Simple pain scores, although providing important information, do not capture the patient's total pain experience, which includes the effect on quality of life.[41] In our study, the improvement in quality of life was considered a major therapeutic target by the two patient representatives a view supported by the expert clinicians within the group and by the research of Almeida et al.[42]

This complex multimodal analgesia exerted by THC is compatible with the ubiquitous distribution of CB_1 receptors in the CNS and the fact that cannabinoids act as complex neuromodulators. It has also been shown that the analgesic effects of THC may be more attributable to its effects on higher cognitive emotional brain mechanisms than its effects on somatosensory processing (antinociception).[43] Clinically, this has been scarcely explored. In one of the two medical cannabis studies including quality of life, Toth et al.[44] highlight that flexible-dose nabilone (1–4 mg/day) was effective in relieving neuropathic pain symptoms, improving disturbed sleep, and overall quality of life. In another small study of 23 participants, Ware et al.[45] found no statistically significant effects on quality of life of smoking cannabis with THC potencies of 0%, 2.5%, and 6%. However, at 9.4% sleep improved. The absence of quality research on quality-of-life studies is disappointing and highlights the need to collect better evidence.

Recognizing the relative paucity of high-quality published data on the three cannabinoid pharmacotherapies, the group conducted a sensitivity analysis whereby scores on pain relief for THC/CBD and THC were halved; but these two cannabinoids still dominated the alternatives. In contrast, when the input preference scores on quality of life were also halved, then duloxetine, the gabapentinoids, and amitriptyline clustered together near or on the efficient curve, leaving the CBMPs well inside.

The Effects Table provides the collective views of the experts, clinicians, and patients who participated in the decision conference, so could be of use to a prescriber wishing to make a better-informed decision for an individual patient. As a general example, if a patient and their clinician are more concerned about quality of life than pain relief, then Table 4 shows that THC/CBD or THC could be the best pharmacotherapy. For patients who are more concerned about pain relief, then duloxetine might be the best choice, as it has a better safety profile than the gabapentinoids

and amitriptyline. The Effects Table makes clear that there is a trade-off to be considered between pain relief and quality of life measures, and that side effect profiles need to be considered. The Effects Table makes all this explicit in a form made possible by MCDA modeling. The data supplied regarding subscores may, therefore, further serve to consider specific desired or undesired effects in patients with specific symptom constellations and/or medical comorbidities.

A main limitation of this study is in the shortage of published data for some of the pharmacotherapies, particularly for the CBMPs (and CBD alone in particular), requiring heavy reliance on participants' judgments about scores. That paucity of data was not only anticipated but was actually the rationale for holding this MCDA meeting and benefitting from the real-world views of an expert panel. Accordingly, participants were carefully chosen for their medical and scientific expertise about neuropathic pain and its treatment, clinical experience in treating patients, knowledge about cannabinoids and CBMPs, and incorporating representatives of patients with CNP who have direct experience themselves with the pharmacotherapies reviewed and were also acquainted with the experiences of other patients using them.

At the end of the decision conference, participants were asked for their views of the MCDA/decision conferencing approach. Most considered the results were a very good way of reaching a joint result about an issue for which there is little data. Several participants thought the group might be biased in favor of the CBMPs. Some participants also thought the group might be biased against opioids although they are widely used (although not usually guideline recommended) in treatment of CNP. It was felt that this may have been particularly influenced by the patient representatives' opinions expressing negative views. Bias is indeed a concern in any study relying on responses from panel members. Fortunately, minimizing or eliminating bias is built into the decision conferencing process by careful selection of participants with diverse views on the key issues and the application by the facilitator of bias-minimizing techniques in eliciting participants' judgments, as had been explained elsewhere.[46,47] We would welcome studies aiming to replicate this research with different groups of experts in different countries. Finally, although we fully acknowledge that this MCDA approach is not a substitute for high-quality clinical trials, it may serve to responsibly share valuable clinical experience, and provide much-needed guidance to prescribers and patients while awaiting publications of better evidence in the field.

Conclusions

What is known about this topic

The value of CBMPs for pain management remains controversial. Some patients and clinicians prefer it to other medications but in the United Kingdom most doctors are reluctant to prescribe because high-quality evidence-based recommendations are lacking, and clinical experience, education, and support are limited. In the absence of persuasive evidence, and in the face of growing clinical use, it is important to obtain the best specialist estimates of the value of the available cannabis-based medicinal products. This is ideally performed by applying MCDA using evidence from RCTs and judgments about the clinical relevance of the evidence to determine the benefit–safety balance of drugs.[48]

What this study has contributed

Our study, the first of its kind, revealed clinically relevant differences in efficacy and adverse effects ratings for a range of different pharmacotherapies used for neuropathic pain. Overall CBMPs of THC/CBD, in a 1:1 ratio, achieved the highest overall score, followed by CBD dominant at 75, then THC dominant at 72. When only benefit measures are considered and not safety measures, the antidepressants (duloxetine and amitriptyline) and the gabapentinoids were rated best for pain control, whereas the THC-containing products scored best for improving quality of life. When safety benefits alone were considered CBD/ibuprofen and THC/CBD came out best.

The current disparity between prescribers' and patients' beliefs in CBMPs medical cannabis may reflect different weightings being given to the relief of pain compared with quality of life. The impact of CBMPs on improving patients' quality of life is increasingly recognized.[49,50] As it emerges that cannabinoids are relatively safe options, certainly compared with other substances used for CNP management, they should be included in the armamentarium of clinical specialists, in line with the recent position article from the European Pain Federation Task Force on the topic.[19] The decision regarding specific patients should take into account existing literature and professional guidelines and, in the face of partial evidence, collective clinical experience. This option should be patient tailored, that is, explored in detail by prescribers and patients together when pharmacological treatment of neuropathic pain is being considered.

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References

1. Nutt D. Why medical cannabis is still out of patients' reach—an essay by David Nutt. BMJ. 2019;365:l1903.
2. Schlag A, Baldwin D, Barnes M, et al. Medical cannabis in the UK: from principle to practice. J Psychopharmacol. 2020;34:931–937.
3. Schlag A. An evaluation of regulatory regimes of medical cannabis: what lessons can be learned for the UK? Med Cannabis Cannabinoids. 2020;3:76–83.
4. Sharon H, Goldway N, Goor-Aryeh I, et al. Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain. J Pain Res. 2018;11:1411–1419.
5. Mirelman D, Waissengrin B, Goldway N, et al. Use of medical cannabis: perceptions of Israeli oncologists. Lancet Oncol. 2019;20:475–477.
6. Couch D. Left behind: the scale of illegal cannabis use for medicinal intent in the UK2020. https://www.thecmcuk.org/left-behind-the-scale-of-illegal-cannabis-use-for-medicinal-intent-in-the-uk (last accessed March 10, 2020).
7. United Patients' Alliance (UPA). UPA Patients' Survey 2018. https://www.upalliance.org/patient-survey-2018 (last accessed April 18, 2020).
8. National Academies of Sciences Engineering and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. The National Academies Press: Washington, DC, 2017.
9. Boychuk DG, Goddard G, Mauro G, et al. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache. 2015;29:7–14.
10. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14:162–173.
11. Petzke F, Enax-Krumova EK, Hauser W. Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: a systematic review of randomized controlled studies. Schmertz. 2016;30:62–88.
12. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456–2473.
13. Stockings E, Campbell G, Hall W, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159:1932–1954.
14. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. Pain. 2020. In Press.

15. Fagerlin A, Zikmund-Fisher BJ, Ubel PA, et al. Measuring numeracy without a math test: development of the Subjective Numeracy Scale. Med Decis Making. 2007;27:672–680.
16. Mücke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018;3: CD012182.
17. Moore RA, Fisher E, Finn DP, et al. Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews. Pain. 2020 [Epub ahead of print]; DOI: 10.1097/j.pain.0000000000001941.
18. Sharon H, Brill S. Cannabis-based medicines for chronic pain management: current and future prospects. Curr Opin Anaesthesiol. 2019;32:623–628.
19. Häuser W, Finn DP, Kalso E, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain. 2018;22:1547–1564.
20. Johal H, Devji T, Chang Y, et al. Cannabinoids in chronic non-cancer pain: a systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13:1–13.
21. Mohiuddin M, Blyth FM, Degenhardt L, et al. General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews. Pain. 2020 [Epub ahead of print]; DOI: 10.1097/j.pain.0000000000002000.
22. Fine P, Cheatle MD. Common adverse effects and complications of long-term opioid therapy. Pain Med. 2015;16 Suppl 1:S1–S2.
23. Onakpoya IJ, Thomas ET, Lee JJ, et al. Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials. BMJ Open. 2019;9:1–19.
24. Riediger C, Schuster T, Barlinn K, et al. Adverse effects of antidepressants for chronic pain: a systematic review and meta-analysis. Front Neurol. 2017;8:1–23.
25. Mohiuddin MM, Mizubuti GB, Haroutounian S, et al. Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guidelines for reporting safety outcomes in trials of medical cannabis and cannabis-based medicines for chronic noncancer pain: a systematic review. Clin J Pain. 2020;36:302–319.
26. Leong J, Salek S, Walker S. Benefit-risk assessment of medicines: the development and application of a universal framework for decision-making and effective communication. Wiley-Blackwell: Chichester, 2012.
27. Phillips LD, Fasolo B, Zafiropoulos N, et al. Is quantitative benefit-risk modelling of drugs desirable or possible? Drug Discov Today Technol. 2011;8:e3–e10.
28. Moore R, Crossley A, Ng B, et al. Use of multicriteria decision analysis (MCDA) for assessing the benefit and risk of over-the-counter analgesics. J Pharm Pharmacol. 2017;69:1364–1373.
29. Vermersch P, Martinelli V, Pfleger C, et al. Benefit-risk assessment of cladribine using multi-criteria decision analysis (MCDA) for patients with relapsing-remitting multiple sclerosis. Clin Ther. 2019;41:249–260.
30. Wright S, Duncombe P, Altman DG. Assessment of blinding to treatment allocation in studies of a cannabis-based medicine (Sativex®) in people with multiple sclerosis: a new approach. Trials. 2012;13:189.
31. Franco LA, Montibeller G. Facilitated modelling in operational research. Eur J Oper Res. 2010;205:489–500.
32. Phillips LD. Decision conferencing. In: Edwards W, Miles RF, von Winterfeldt D, eds. Advances in decision analysis: from foundations to applications. Cambridge University Press: Cambridge, 2007.
33. European Medicines Agency. Benefit-risk methodology project; Work package 4 report: benefit-risk tools and processes. European Medicines Agency: London, 2012.
34. Hughes D, Waddingham E, Mt-Isa S, et al. Recommendations for benefit-risk assessment methodologies and visual representations. Pharmacoepidemiol Drug Saf. 2016;25:251–262.
35. Phillips LD. Benefit-risk modeling of medicinal products: methods and applications. In: Sashegyi A, Felli J, Noel R, eds. Benefit-risk assessment in pharmaceutical research and development. CRC Press: Boca Raton, FL, 2014: pp. 59–96.
36. LSE/Catalyze. 2011. Hiview3 www.catalyzeconsulting.com. (last accessed October 1, 2019).
37. Montibeller G, von Winterfeldt D. Cognitive and motivational biases in decision and risk analysis. Risk Anal. 2015;25:1230–1251.
38. Tervonen T, Gelhorn H, Bhashyam SS, et al. MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. Pharmacoepidemiol Drug Saf. 2017;26:1483–1491.
39. von Winterfeldt D, Edwards W. Decision analysis and behavioral research. Cambridge University Press: Cambridge, 1986.
40. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10:287–333.
41. Rowbotham DJ. Neuropathic pain and quality of life. Eur J Pain. 2002;6 Suppl B:19–24.
42. Almeida FC, Castilho A, Cesarino CB, et al. Correlation between neuropathic pain and quality of life. Br J Pain. 2018;1:349–353.
43. Weizman L, Dayan L, Brill S, et al. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. Neurology. 2018; 91:e1285–e1294.
44. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153:2073–2082.
45. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182:E694–E701.
46. Nutt DJ, Phillips LD, Balfour D, et al. E-cigarettes are less harmful than smoking. Lancet. 2016;387:1160–1161.
47. Phillips LD. Best practice for MCDA in healthcare. In: Marsh K, Goetghebeur M, Thokala P, Baltussen R, eds. Multi-criteria decision analysis to support healthcare decisions. Springer International Publishing AG, New York, 2017: pp. 311–329.
48. Thokala P, Devlin N, Marsh K, et al. Multiple criteria decision analysis for health care decision making—an introduction: report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Health. 2016;19:1–13.
49. Lavie-Ajayi M, Shvartzman P. Restored self: a phenomenological study of pain relief by cannabis. Pain Med. 2018;20:2086–2093.
50. Russo EB. Cannabis and pain. Pain Med. 2019;20:2083–2085.

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Abbreviations Used

AEs = adverse events
CBMPs = cannabis-based medical products
CI = confidence interval
CMC = Centre for Medical Cannabis
CNP = chronic neuropathic pain
DDS = descriptor differential scale
DPN = diabetic peripheral neuropathy
EMA = European Medicines Agency
GI = gastrointestinal
IQR = interquartile range
MCDA = multicriteria decision analysis
NASEM = National Academies of Sciences, Engineering and Medicine
NNT = number needed to treat
NRS = numerical rating scale
PNP = peripheral neuropathic pain
RCT = randomized control trial
SAEs = serious adverse events
SGIC = Subject Global Impression of Change
THC/CBD = tetrahydrocannabinol/cannabidiol
VAS = visual analog scale

(*Appendix follows* →)

Appendix Table A1. Randomized Control Trials on the Use of Medical Cannabis for Chronic Neuropathic Pain

Title	Year	Authors	CBMP	Condition	Results
A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms	2003	Wade DT, Robson P, House H, Makela P, Aram J.	Whole-plant extracts of THC, CBD, 1:1 CBD:THC, or matched placebo	Mixed: multiple sclerosis (18), spinal cord injury (4), brachial plexus damage (1), and limb amputation due to neurofibromatosis (1)	Pain relief associated with both THC and CBD was significantly superior to placebo.
Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial	2004	Berman JS, Symonds C, Birch R.	Sativex (THC:CBD) or THC	Neuropathic pain from brachial plexus avulsion	The pain rating index and VAS were significantly improved by THC ($p=0.04$) but not Sativex. The pain review score, sleep quality and sleep disturbance scores were significantly improved by both THC and Sativex.
Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 '*N* of 1' studies	2004	Nottcut W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C.	THC, CBD, 1:1 CBD:THC	CNP	Extracts which contained THC proved most effective in symptom control.
Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis	2005	Rog D, Nurmikko T, Friede T, Young C.	Whole plant THC:CBD delivered through oromucosal spray, each spray delivered 2.7 mg of THC and 2.5 of CBD.	Central pain in multiple sclerosis	CBMP was superior to placebo in reducing the mean intensity of pain (CBMP mean change −2.7, 95% CI: −3.4 to −2.0, placebo −1.4 95% CI: −2.0 to −0.8, comparison between groups, $p=0.005$) and sleep disturbance (CBMP mean change −2.5, 95% CI: −3.4 to −1.7, placebo −0.8, 95% CI: −1.5 to −0.1, comparison between groups, $p=0.003$).
Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial	2007	Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D.	Sativex (THC:CBD)	Unilateral PNP and allodynia	The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving Sativex than placebo (mean adjusted scores −1.48 points vs. −0.52 points) on a 0–10 Numerical Rating Scale ($p=0.004$; 95% CI: −1.59 to −0.32). Improvements in Neuropathic Pain Scale composite score ($p=0.007$), sleep NRS ($p=0.001$), dynamic allodynia ($p=0.042$), punctate allodynia ($p=0.021$), Pain Disability Index ($p=0.003$) and Patient's Global Impression of Change ($p<0.001$) were similarly greater on Sativex versus placebo.

(*continued*)

Appendix Table A1. (Continued)

Title	Year	Authors	CBMP	Condition	Results
Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial	2007	Abrams D, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL.	Smoked cannabis	Painful HIV-associated sensory neuropathy	Smoked cannabis reduced daily pain by 34% (median reduction; IQR = −71 to −16) versus 17% (IQR = −29 to 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% versus 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p \leq 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation.
A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain	2008	Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S.	Cannabis cigarettes	Neuropathic pain	No effect on evoked pain was seen.
Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial	2009	Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley	Cannabis cigarettes	HIV-associated distal sensory predominant polyneuropathy	Among the completers, pain relief was greater with cannabis than placebo (median difference in DDS pain intensity change, 3.3 points, effect size = 0.60; $p = 0.016$). The proportions of subjects achieving at least 30% pain relief with cannabis versus placebo were 0.46 (95% CI: 0.28 to 0.65) and 0.18 (0.03 to 0.32).
Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor	2010	Selvarajah D, Gandhi R, Emery CJ, Tesfaye S.	Sativex (THC:CBD)	Painful diabetic neuropathy	There was significant improvement in pain scores in both groups, but mean change between groups was not significant. Depression was a major confounder and may have important implications for future trials on painful DPN.
Smoked cannabis for chronic neuropathic pain: a randomized controlled trial	2010	Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP.	Smoked cannabis	CNP: (post-traumatic or postsurgical)	The average daily pain intensity, measured on the 11-point numeric rating scale, was lower on the prespecified primary contrast of 9.4% versus 0% THC (5.4 vs. 6.1, respectively; difference = 0.7, 95% CI: 0.02 to 1.4). Preparations with intermediate potency yielded intermediate but nonsignificant degrees of relief. Participants receiving 9.4% THC reported improved ability to fall asleep (easier, $p = 0.001$; faster, $p < 0.001$; more drowsy, $p = 0.003$) and improved quality of sleep (less wakefulness, $p = 0.01$) relative to 0% THC.

(*continued*)

Appendix Table A1. (Continued)

Title	Year	Authors	CBMP	Condition	Results
An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain	2012	Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestard J, Korngut L.	Nabilone (THC)	Diabetic PNP	For nabilone run-in-phase responders, there was an improvement in the change in mean end-point neuropathic pain versus placebo (mean treatment reduction of 1.27; 95% CI: 2.29 to 0.25, $p=0.02$), with an average nabilone dose at end-point of 2.9 ± 1.1 mg/day, and improvements from baseline for the anxiety subscale of the Hospital Anxiety and Depression Scale, the Medical Outcomes Study sleep scale problems index, and the European Quality of Life-5-Domains index score (each $p<0.05$). Nabilone run-in-phase responders reported greater global end-point improvement with nabilone than with placebo (100% vs. 31%; $p<0.05$).
Low-dose vaporized cannabis significantly improves neuropathic pain	2013	Wilsey B, Marcotte TD, Deutsch R, Gouaux B, Sakai S, Donaghe H.	Vaporized cannabis	Experiencing neuropathic pain despite traditional treatment	A treatment effect was noted with cumulative dosing, with the magnitude of differences between the doses changing over time (treatment by time interaction: $p=0.0133$). Significant separation occurred at 120 min ($p=0.0002$). The NNT to achieve 30% pain reduction was 3.2 for placebo versus low dose, 2.9 for placebo versus medium dose, and 25 for medium versus low dose.
A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment	2014	Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E	Sativex (THC:CBD)	PNP associated with mechanical allodynia	At the 30% responder level, there were statistically significant treatment differences in favor of THC/CBD spray in the full analysis (intention-to-treat) data set ($p=0.034$; 95% CI: 1.05 to 3.70). There was also a reduction in mean PNP 0–10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance. Secondary measures of sleep quality 0–10 NRS score ($p=0.0072$) and SGIC ($p=0.023$) also demonstrated statistically significant treatment differences in favor of THC/CBD spray treatment.

(*continued*)

Appendix Table A1. (Continued)

Title	Year	Authors	CBMP	Condition	Results
The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study	2014	Eisenberg E, Ogintz M, Almog S.	Cannabis flower	Sufferers of neuropathic pain of any type	A significant 45% reduction in pain intensity was noted 20 min postinhalation ($p = 0.001$), turning back to baseline within 90 min.
A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain	2015	Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejčko J, Taylor L	Sativex (THC:CBD)	PNP associated with diabetes or allodynia	Decrease in pain score over time. At least half of patients had a 30% improvement in pain at all time points. Sustained improvements from baseline were also observed in NPS and sleep quality scores. Also no evidence of a tolerance developing toward THC/CBD spray.
An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease	2016	Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A.	Vaporized cannabis	Individuals with injury or disease of the spinal cord	Using an 11-point numerical pain intensity rating scale as the primary outcome, a mixed effects linear regression model showed a significant analgesic response for vaporized cannabis. When subjective and psychoactive side effects (e.g., good drug effect and feeling high) were added as covariates to the model, the reduction in pain intensity remained significant above and beyond any effect of these measures (all $p < 0.0004$).

CBMP, cannabis-based medical product; CBD, cannabidiol; CI, confidence interval; CNP, chronic neuropathic pain; DDS, descriptor differential scale; DPN, diabetic peripheral neuropathy; IQR, interquartile range; NNT, number needed to treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; SGIC, Subject Global Impression of Change; THC, tetrahydrocannabinol; VAS, visual analog scale.

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Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis

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Background: Chronic neuropathic pain (NP) presents therapeutic challenges. Interest in the use of cannabis-based medications has outpaced the knowledge of its efficacy and safety in treating NP. The objective of this review was to evaluate the effectiveness of cannabis-based medications in individuals with chronic NP.
Methods: Randomized placebo-controlled trials using tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidivarin (CBDV), or synthetic cannabinoids for NP treatment were included. The MEDLINE, Cochrane Library, EMBASE, and Web of Science databases were examined. The primary outcome was the NP intensity. The risk of bias analysis was based on the Cochrane handbook.
Results: The search of databases up to 2/1/2021 yielded 379 records with 17 RCTs included (861 patients with NP). Meta-analysis showed that there was a significant reduction in pain intensity for THC/CBD by −6.624 units ($P < .001$), THC by -8.681 units ($P < .001$), and dronabinol by -6.0 units ($P = .008$) compared to placebo on a 0−100 scale. CBD, CBDV, and CT-3 showed no significant differences. Patients taking THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain ($P = .008$) and 1.422 times more likely to achieve a 50% reduction ($P = .37$) than placebo. Patients receiving THC had a 21% higher improvement in pain intensity ($P = .005$) and were 1.855 times more likely to achieve a 30% reduction in pain than placebo ($P < .001$).
Conclusion: Although THC and THC/CBD interventions provided a significant improvement in pain intensity and were more likely to provide a 30% reduction in pain, the evidence was of moderate-to-low quality. Further research is needed for CBD, dronabinol, CT-3, and CBDV.

Keywords: Cannabidiol; Cannabis; Meta-Analysis; Neuropathic Pain; Systematic Review.

INTRODUCTION

Neuropathic pain (NP) is described by the International Association for the Study of Pain (IASP) as "Pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system" [1]. NP occurs as a result of a pathological maladaptive reaction of the nervous system to damage or injury, and is sometimes described as pain being felt in the absence of afferent nociceptive input or noxious stimuli that are typically interpreted at the cortical level of the brain as pain [2].

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Causes of NP include multiple sclerosis (MS), diabetes, cancer, spinal cord injury, HIV infection, shingles, and stroke, as well as other conditions, such as trigeminal neuralgia (TN), amputation, traumatic or postsurgical nerve injuries, peripheral nerve injury, leprosy, and lumbar or cervical radiculopathies [2,3]. NP impairs the overall quality of life by negatively affecting work performance, influences social relationships, and significantly impacts the healthcare system [4].

NP can be found in many areas of the somatosensory nervous system. It can be acute or chronic, continuous or episodic, and spontaneous or evoked by typically non-painful stimuli. The intensity and pattern can vary between individuals and within individuals [5]. NP can be mediated and maintained by both central and peripheral mechanisms that cause dysfunction in the transmission and processing of neural stimuli within the somatosensory system [5]. Mechanisms implicated in NP include alterations in ion channels, imbalances between excitatory and inhibitory somatosensory signaling, and the variable ways in which pain signals are modified in the central nervous system (CNS) [2]. Central sensitization is an important contributor to persistent pain and allodynia, which is common in chronic NP by altering the sensory reaction produced by normal stimuli, including signals that would normally produce innocuous sensations [6]. The variability of the clinical presentation and symptoms along with the possible involvement of CNS dysfunction have made the treatment of NP a challenge for clinicians. Therefore, it often requires a multimodal and multidisciplinary approach for management [2].

1. Cannabis interventions

Existing evidence suggests that the Cannabis plant has been used by humans for hundreds of years for various purposes, including its therapeutic properties, such as pain relief; appetite stimulation; alleviation of fatigue, anger, and fear; and the treatment of epilepsy [7,8]. In 1970, the Controlled Substances Act made it unlawful to grow and sell hemp and marijuana in the United States (USA), thereby limiting the possibility to explore its properties. Progressive social and political changes in the USA and other countries and the passing of the 2014 Agricultural Act, which differentiated hemp and marijuana's legality, has allowed researchers to investigate the benefits of cannabis and its potential therapeutic use for the management of several medical conditions, including chronic NP [9].

Cannabis is a genus of plants in the Cannabaceae family [10]. Two recognizable species within the cannabis genus are *Cannabis sativa* and *Cannabis indica*, and are known as marijuana [11]. Marijuana and hemp are two strains of *C. sativa*; marijuana is cultivated mainly for its delta 9-tetrahydrocannabinol (delta 9-THC) content, and hemp for its usefulness in the production of industrial products such as clothing, paper, oil, and food [12]. The scientific investigation of *C. sativa* has made significant progress in the past 35 years, as the numerous active ingredients of *C. sativa* strains have been identified, and major breakthroughs have been made concerning the human body's endogenous cannabinoids (CBs) and the endocannabinoid system (ECS) with its regulatory functions in health and disease [13].

The ECS is the pathway by which tetrahydrocannabinol (THC) and other CBs interact in an animal's body. Prior research has shown that CB receptors and ligands are present in the bone, immune system, peripheral nervous system, and CNS [14]. Studies have shown that the ECS has three functions in mammals [15]. The first function affects stress recovery in animals, acting in a feedback loop where endocannabinoid signaling is activated by stress and acts to return nervous, behavioral, and endocrine systems to a homeostatic balance [16]. The second role is thought to regulate the body's energy balance through regulation of food intake, utilization, and storage [17]. The third function involves immune system tasks, whereby endocannabinoid signaling is activated by tissue injury [18] and modulates immune and inflammatory responses [19]. Thus, the ECS is involved in multiple homeostatic and physiological functions, such as antinociception, inflammation, cognition and memory,

nausea and vomiting, endocrine function, and immune system recognition [20].

Cannabis reportedly contains over 450 compounds, with 70 classified as phytocannabinoids. Delta 9-THC is the main active component, with psychoactive (e.g., reduction of anxiety and stress) and pain-relieving properties. Cannabidiol (CBD) is another component of interest. Studies have shown that CBD has a lower affinity for CB receptors and may counteract the undesirable effects of THC on memory, cognition, and mood, but may also have an effect on pain modulation by anti-inflammatory properties [21]. The specific functions of the identified cannabinoids that act as ligands at CB receptors within the nervous system have only been partially elucidated [14]. However, according to data from prior pharmacological studies and research using CB receptor knock-out mice, the mechanisms involved in the analgesic effects of CBs are thought be based on the activation of CB1 and/or CB2 receptors, causing a decrease in pain signal transmission and/or anti-inflammatory effects [22–24]. Two major endocannabinoids described so far, 2-arachidonylglycerol and anandamide, have been shown to influence the transmission of pain signals by acting on CB1 and CB2 receptors [22]. Additionally, these endogenous receptors in humans may play a role in reducing changes in cognitive and autonomic processing in chronic pain states [25].

Preclinical data demonstrate that the CB1 receptor is expressed in regions of the CNS, such as the dorsal root ganglia [26], periaqueductal gray area and nucleus raphe [27,28], dorsal horn of the spinal cord [29], and forebrain [30]. Additionally, evidence from several animal models demonstrates an upregulation of CB receptors in the CNS following nerve injury, suggesting a role of cannabinoids in the possible treatment of NP conditions [31–33]. Studies examining plant-based and synthetic cannabis-based interventions have provided data suggesting the use of cannabis-based medications as a possible approach for the management of chronic NP of different origins [34].

Given the current challenges in the treatment of chronic NP in combination with the ongoing fear of the long-term effects of the opioid epidemic, chronic pain management physicians as well as orofacial pain specialists need more innovative, effective, and safer options to alleviate NP [35]. Although opiates and non-steroidal anti-inflammatory medications are the primary pharmacological treatments for nociceptive pain, these medications have a modest effect and only in a minority of patients with NP due to the inability to precisely target the underlying mechanisms [36]. High-potency opioids have a number needed to treat one patient to experience a reduction of pain by at least 50% (NNTB) of 4.3 NP (NNTB 3.4-5.8) [37]. Current pharmacological treatments for chronic NP have largely been limited to tricyclic antidepressants (TCAs) and neuromodulators (i.e., sodium channel blockers and anticonvulsants), but these have also only shown partial efficacy in most patients [38], with a NNTB for these first-line drugs falling in the range of 3.5 to 7.7 for one patient to achieve at least a 50% reduction in pain [37]. Individuals with chronic NP conditions struggle to find effective treatment options and often undergo multiple trials with commonly used medications in search for an effective treatment and relief. The financial, social, psychological, and physical toll that poorly treated chronic NP can contribute significantly. Individuals with painful neuropathic disorders show a three-fold increase in healthcare costs compared to the matched control groups [39]. The prevalence of NP in the general population has been reported to be between 7% and 10% in some countries [2,40].

There is a need to explore additional treatment options for NP; with the increasing awareness and use of cannabinoids for medical purposes, a systematic review with meta-analysis is needed to summarize its effectiveness and safety as a therapeutic option for the treatment of chronic NP.

2. Objectives

The objective of this systematic review and meta-analysis was to evaluate the effectiveness of cannabis-based medications, including herbal cannabis

(marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), and pharmacological synthetic cannabinoids (e.g., nabilone, CT-3), as therapeutic agents compared to placebo intervention (i.e., cigarettes with 0% cannabis) in patients with chronic NP.

METHODS

1. Research question

This study follows the preferred reporting elements for systematic reviews and meta-analyses (PRISMA) guidelines [41], and the procedure was registered with PROSPERO #CRD42021234766. The PICOS question was:

- Population: Individuals diagnosed with NP (central NP, cancer-related neuropathy, painful diabetic neuropathy, complex regional pain syndrome (CRPS) type II, postherpetic neuralgia (PHN), peripheral polyneuropathy of other etiologies, trigeminal neuralgia; HIV neuropathy, spinal cord injury; postoperative or traumatic peripheral nerve lesions due to trauma; nerve plexus injury and phantom limb pain).
- Intervention: Cannabis-based medications, either herbal forms of cannabis (marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), or pharmacological (synthetic) cannabinoid formulations (e.g., nabilone, CT-3). Any route of administration (i.e., smoking, vaping, oral administration)
- Comparison: Placebo intervention.
- Primary outcomes: NP intensity and spontaneous pain intensity at baseline and post-treatment or reduction post-treatment.
- Secondary outcomes: Other pain outcomes, quality of life, cognitive decline assessment, sleep quality, qualitative testing, disability status, rescue medications, and adverse events or side effects.
- Setting: Orofacial pain clinic, university hospital, or clinical care center.

2. Inclusion and exclusion criteria

The studies included in this systematic review were limited to publications in English of randomized placebo-controlled trials. Studies identified with no placebo control, abstract only, not in English, with conditions other than NP, where cannabinoid medications were adjuvant only, and duplicate studies were excluded from this review.

3. Search methods for identification of studies

Four electronic databases (EMBASE, MEDLINE through PubMed, Web of Science, and Cochrane) were searched up to 2/1/2021 using the strategies described in Table 1.

4. Data collection and analysis

After removing duplicates, the references were screened by three authors (J.B., B.S., M.P.). The titles and abstracts of all records were analyzed using the inclusion and exclusion criteria. If there was no agreement among the reviewers, the full PDF was retrieved and analyzed. The reference sections of all literature reviews, systematic reviews, meta-analyses, and clinical guidelines in addition to all eligible RCTs were then scanned by three authors (J.B., B.S., M.P.) for any further applicable references. Any new relevant study was screened using the same inclusion and exclusion criteria and subsequently reviewed by the same three authors. If a consensus was not reached by the authors, the full article was reviewed, and a fourth author (R.E.) was involved if there was no consensus.

5. Data Extraction and Management

Three authors (J.B., B.S., M.P.) independently extracted the data obtained from the identified RCTs. Data included participants' demographics, control groups, intervention groups, funding, and outcomes. Any disagreement among the three authors (J.B., B.S., M.P.) was reviewed and resolved by consensus with a fourth author (R.E.).

Table 1. Electronic database search strategies

Electronic database	Search strategy
MEDLINE via PubMed (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	**Language: limited to English** **Species: limited to Humans** **Article types: limit to Clinical Trails, Randomized Controlled Trials, Review, Systematic Reviews, Guidelines, Meta-analysis, Practice Guideline** ((neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND ("Cannabis" [Mesh] OR "Medical Marijuana" [Mesh] OR "Cannabidiol" [Mesh] OR "Cannabinoids" [Mesh] OR marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid* OR hash* OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol OR THC)) AND random*
The Web of Science (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	TOPIC: (neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND TOPIC: (marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid* OR hash* OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol) AND TOPIC: random* Limits: Article, Review, Proceedings, Early Access
The Cochrane Library (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	((neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy)) AND (marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid OR hash OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR delta9-tetrahydrocannabinol OR delta-9-tetrahydrocannabinol OR THC)) AND (random OR randomly OR randomized)
EMBASE (searched up to 2/5/2020); re-run on 2/1/2021 search strategy:	#1 neuralgia OR neuropathy OR neuropathic OR (nerve AND (injury OR lesion)) OR (post-herpetic neuralgia) OR (post-traumatic neuropathy) #2 marijuana OR marihuana OR cannabis OR cannabidiol OR cannabinoid OR hash OR hemp OR nabilone OR dronabinol OR nabiximols OR Sativex OR levonantradol OR sativa OR tetrahydrocannabinol OR "delta9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" #3 randomly OR randomized OR random #4: #1 and #2 and #3 Limits: English, Article, Article in Press, Conference paper,

6. Assessment of risk of bias in included studies

The risk of bias for each eligible trial was independently identified by three reviewers (J.B., B.S., M.P.) and reviewed by a senior author (R.E.), following the recommended guidelines in the Cochrane Handbook [42].

7. Statistical analyses

RCTs on cannabis-based medications compared to placebo groups for NP were included. Means and standard deviations (SD) were calculated based on reported medians (m) and interquartile range (IQR) = (q1, q3), with q1 = 25% quartile, and q3 = 75% quartile, as: mean = (q1 + m + q3)/3; SD = (q3 − q1)/ 1.35. SD was calculated based on the reported standard error of the mean (SEM) as follows: SD = SEM × sqrt (N), where N is the total sample size in the intervention group. For pain intensity, outcomes reported on a 0–10 scale were converted to a 0-100 scale by multiplying by 10.

Treatment effects for pain intensity reported on a 0–100 Visual Analog scale (VAS) or a 0-100 Numerical Rating scale (NRS) were expressed as the difference in means (DM) of the change in outcomes from baseline with 95% confidence intervals (CI). Treatment effects for percent reduction in NP intensity from baseline as well as post-treatment pain disability scores, McGill pain questionnaires, and SF-36 were reported as DM of post-treatment outcomes with 95% CI. For the number of patients with 30% (or 50%) reduction in pain intensity, treatment effects were expressed as risk ratios (RR) with 95% CI.

Cochran's Q test [43] and the I2 statistic [44] were used to test for heterogeneity. A random-effects model was employed when there was heterogeneity (Q-test P<.10); otherwise, a fixed-effect model was used. All statistical analyses were performed using the Comprehensive Meta-Analysis v3 software. (Biostat, Englewood, NJ, USA). Statistical significance was defined as $P \leq .05$.

8. Subgroup and sensitivity analyses

Sensitivity analyses for low risk of bias versus

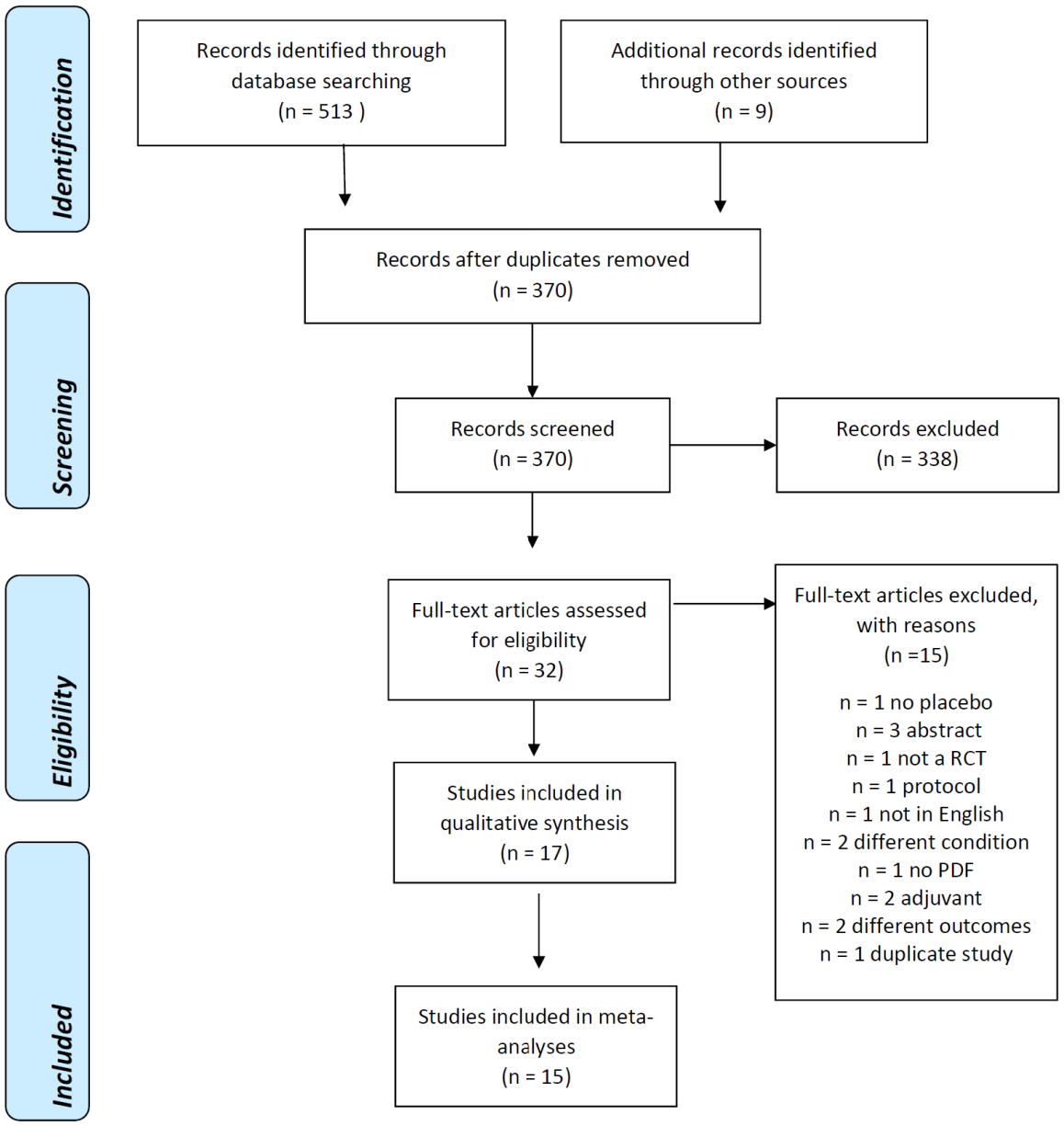


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram [42]. RCT, randomized controlled trials, PDF, portable document format.

unclear/high risk of bias due to the small number of studies could not be conducted, nor a funnel plot to assess for publication bias. Subgroup analyses were conducted for THC/CBD, THC, CBD, cannabidivarin (CBDV), and synthetic cannabis therapies (dronabinol, CT-3).

9. Quality of the evidence

A summary of the quality of the evidence was obtained using the GRADE profiler software (GRADEpro), following the GRADE Working Group guidelines [45].

RESULTS

1. Results of the search

The initial search strategy through databases on February 5, 2020, yielded 513 references, and 9 additional references identified through a manual search. After duplicates were removed, 370 records were screened and reduced to 32 relevant manuscripts. These manuscripts were searched for full-text availability and analyzed for

Table 2. Summary of eligible studies

Reference	Year, Country	Study design, Total sample size	Interventions, sample size per group	Delivery	Tx duration	Washout period for crossover studies	Gender (M/F)	Age (Mean ± SD or range in years)
Abrams, et al. 2007 [63]	2007, USA	DBRPCT parallel design N = 55	• 3.56% THC cigarettes (n = 27) • 0% THC cigarettes (n = 28)	Smoked	5 d	N/A	48M/7F	Tx group: 50 ± 6 Placebo 47 ± 7
Almog, et al. 2020 [47]	2020, Israel	Crossover DBRPC N = 27	• 0.5 mg single inhalation of Δ9-THC • 1 mg single inhalation of Δ9-THC • 0% THC Placebo matched	Inhaler	3 x 150 min sessions	2 d washout	8F/19M	48.3 ± 11.9
Berman, et al. 2004 [49]	2004, England	DBRPCT Crossover N = 48	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100 mL) spray • 2.7 mg THC oromucosal spray • Placebo spray	Spray	14 d	No washout	46M/2F	Mean: 39 23-63
Eibach, et al. 2020 [48]	2020, German	RDBPC Crossover N = 32	• 400 mg/daily oral dose CBDV dissolved in sesame oil • Identical appearing placebo dissolved in sesame oil	Oil	4 weeks	3 weeks washout	31M/1F	CBDV: 52.31 ± 8.06 36-65 Placebo: 48.31 ± 9.62 31-65
Ellis, et al. 2009 [56]	2009, USA	DBRPCT Crossover N = 34	• 1% to 8% THC cigarettes 5xday • Placebo cigarettes 5Xday	Smoked	5 d	2 weeks washout	34M/0F	48.8 ± 6.8
Karst, et al. 2003 [57]	2003, Germany	Crossover study N = 21	• CT-3, 10 mg oral capsules (synthetic THC analog without the psychotropic effects) • Placebo capsules	Oral capsules	1 week	1 week washout	13M/8F	29-65
Nurmikko, et al. 2007 [58]	2007, UK & Belgium	DBRPCT parallel N = 125	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 63) • Placebo spray (n = 62)	Spray	5 weeks	N/A	50M/74F (one patient censored)	Tx group: 52.4 ± 15.8 Placebo: 54.3 ± 15.2
Selvarajah, et al. 2010 [50]	2010, United Kingdom	DBRPCT parallel N = 29	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 15) • Placebo spray (n = 14)	Spray	10 weeks	N/A	18M/11F	Tx group: 58.2 ± 8.8 Placebo: 54.4 ± 11.6
Serpell, et al. 2013 [61]	2013, United Kingdom, Czech Republic	DBRPCT parallel N = 246	• Sativex (THC 2.7 mg & CBD 2.5 mg per 100mL) spray (n = 128) • Placebo spray (n= 118)	Spray	14 weeks	N/A	96M/150F	Tx group: 57.6 ± 14.4 Placebo: 57.0 ± 14.1
Svendsen, et al. 2004 [51]	2004, Denmark	RDBPCT Crossover N = 24	• Dronabinol 2.5 mg capsules (n = 24) • Placebo sesame seed oil capsule (n = 24)	Oral capsules	18-21 d	21 d	10M/14F	Median: 50 23-55
Wade, et al. 2002 [60]	2002, United Kingdom	DBRPC Crossover N = 20	• 2.5 mg THC & 2.5 mg CBD spray • 2.5 mg THC spray • 2.5 mg CBD spray • Placebo spray	Spray	2 weeks	None	10M/10F	Mean: 48
Wallace, et al. 2015 [52]	2015, USA	DBRPC Crossover N = 16	• 7% THC Vaporized cannabis • 4% THC Vaporized cannabis • 1% THC Vaporized cannabis • 0% Vaporized cannabis	Vaporized	4 x 4 hours	2 week	9M/7F	56.9 ± 8.2
Ware, et al. 2010 [62]	2008, USA	RDBPCT Crossover N = 23	• 2.5% THC • 6.0% THC • 9.4% THC • Placebo 0% THC	Inhaled - pipe	5 d	9 d	11M/12F	45.4 ± 12.3 25–77
Wilsey, et al. 2008 [53]	2008, USA	RDBPC Crossover N = 38	• 7% THC • 3.5% THC • 0% THC	Inhaled cigarettes	3 x 6-hour sessions	3 d	20M/18F	Mean: 46 21-71
Wilsey, et al. 2013 [54]	2013, USA	DBRPCT Crossover N = 39	• 3.53% THC • 1.29% THC • Placebo cannabis	Inhaled vapor	3 x 6-hour sessions	3 d	28M/11F	50 ± 11
Wilsey, et al. 2016b [55]	2016, USA	DBRPCT Crossover N = 42	• 0% delta 9-THC, • 2.9% delta 9-THC • 6.7% delta 9-THC	Inhaled vapor	3 x 8-hour sessions	3 d	29M/13F	46.4 ± 13.6
Wilsey, et al. 2016a [59]	2016, USA	RPCT Crossover N = 42	• 6.7% THC cannabis • 2.9% THC cannabis • 0% THC cannabis	Inhaled vapor	3 x 8-hour sessions	3 d	29M/13F	Mean: 46.4

Abbreviations: CBD, cannabidiol; CBDV, cannabidivarin; CRPS, Complex Regional Pain Syndrome; d, day; DBRPCT, Double-blind Randomized Placebo-Controlled Trial; F, female; N, participants; n, participants; NP, Neuropathic pain; M, male; RPCT, Randomized Placebo-Controlled Trial; THC, tetrahydrocannabinol; y, years.

inclusion. Seventeen studies were found to be relevant for inclusion. The main reasons for exclusion were no placebo group (n = 1), abstract proceedings (n = 3), not an RCT (n = 1), protocol (n = 1), not in English (n = 1), not NP (n = 2), no PDF available (n = 1), adjuvant to other treatments (n = 2), different outcomes such as side effects (n = 2), and duplicate studies (n = 1) [46]. All four databases were searched again on February 1, 2021, and two additional references [47,48] were found. The PRISMA flowchart shows a summary of the search and screening results (Fig. 1).

2. Included studies

Seventeen references were included in the qualitative analysis [47–63], as shown in Table 2. Four studies followed an RCT parallel design [50,58,61,63], and 13 studies followed a crossover design [47,48,59,60,62,49,51–57].

1) Types of NP

- Three studies included patients with symptomatic HIV-associated sensory neuropathy [48,56,63].
- Seven studies included patients with NP associated with nerve injury [49,53–55,57,59,62].
- One study reported unilateral peripheral neuropathic pain (PNP) and allodynia [58].
- Two studies included patients with painful diabetic neuropathy (PDN) symptoms [50,52].
- Two studies reported mechanical allodynia and at least one of the following: radiculopathy, complex regional pain syndrome (CRPS) type 2, post-herpetic neuralgia (PHN), and peripheral neuropathy [47,61].
- One study reported that NP was associated with multiple sclerosis (MS) [51].
- One study included patients with a neurological diagnosis of NP pain associated with muscle spasm and tremor, including spinal cord injury (n = 4), brachial plexus damage (n = 1), multiple sclerosis (n = 18), and limb amputation (n = 1) [60].

2) Diagnosis of NP

NP was diagnosed using the following tools (Table 3):

- The diagnosis of NP varied among the studies and was based on clinical symptoms, according to the IASP 2008 criteria [64], Douleur Neuropathique 4 interview (DN4i) [40], Leeds Assessment of Neuropathic Symptoms and Signs [65], and Neuropathy Total Symptom Score 6 [66].
- CRPS was diagnosed using Budapest criteria [67] in one study [47].
- HIV-associated NP was diagnosed using the clinical HIV-associated neuropathy tool [68].
- One study [61] included patients with mechanical allodynia and hyperalgesia with PHN, peripheral neuropathy, focal nerve lesion radiculopathy, or CRPS type II.
- Diagnosis of multiple sclerosis was based on clinical symptoms and laboratory supported diagnosis.
- Painful diabetic peripheral neuropathy was diagnosed using the Michigan Neuropathy Screening Instrument [69].

3) Population

The ages of the participants ranged from 21 to 77 years. The number of participants ranged from a minimum of 16 [52] to 246 research subject [61]. RCTs were conducted in the USA [52–56,59,62,63], Israel [47], and Europe and the UK [48–51,57,58,60,61] (Table 2). Centers providing the intervention varied from pain clinical research centers [47,53,54], university hospitals [49–52,56,58,61,62], and medical schools [55,57,59].

4) Interventions

Cannabinoid medications were administered via a variety of methods and in various dosage forms (Table 2).

- THC/CBD: Oromucosal spray Sativex containing 2.7 mg of THC and 2.7 mg of CBD [49,50,58,61] or a spray containing 2.5 mg of THC and CBD [60].
- THC:
  - Three of the included studies used cannabis cigarettes [53,56,63] with THC varying from 1% to 8%.

Table 3. Diagnosis of neuropathic pain and inclusion criteria

Reference	Dx of NP	Inclusion criteria
Abrams, et al. 2007 [63]	(1) Adults with HIV infection and symptomatic HIV-SN (2) Painful HIV-SN was confirmed by symptoms of symmetric distal pain or dysesthesias in the lower extremities for at least 2 weeks, combined with absent or depressed ankle reflexes or sensory loss of vibration, pin, temperature, or touch on examination by the study neurologist.	(1) Average daily pain score of at least 30 mm on the 100 mm VAS during the outpatient pre-intervention phase. (2) Patients were in stable health. (3) Without current substance abuse (including tobacco) (4) Followed a stable medication regimen for pain and HIV for at least 8 weeks prior to enrollment, (5) All patients were required to have prior experience smoking cannabis.
Almog, et al. 2020 [47]	The diagnoses of NP and CRPS were made by an investigating physician according to IASP 2008 [64], and Budapest criteria [67], respectively.	(1) Adult patients (18 years of age or above), (2) Suffering from chronic pain with a baseline pain intensity of 6 or above on a 10-cm visual analog scale (VAS), (3) Licensed by the Israeli Ministry of Health to receive cannabis-based medications. (4) Active users had to agree to abstain from cannabis-based medications 12 hr. before study intervention. (5) Women of fertile age had to declare using contraception.
Berman, et al. 2004 [49]	(1) At least one avulsed brachial plexus injury (2) at least 18 months duration	(1) Men/women 18 + (2) Stable pain pattern 4 + weeks (3) Stable medication regimen 4 + weeks and during study (4) No cannabis use at least 7 days prior to study
Eibach, et al. 2020	The diagnosis of HIV-associated sensory neuropathy was confirmed by a clinician based on: • patient history, • the Douleur Neuropathique 4 interview (DN4i) [40] • the Clinical HIV-associated Neuropathy Tool [68].	(1) 18 - 65 years old (2) Pain > 4 on a NRS (0 - 10)
Ellis, et al. 2009 [56]	(1) HIV-DSPN diagnosed by a board-certified clinical neurologist included: • the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or • electrophysiological abnormalities (distal leg sensory nerve conduction studies), • symptoms of pain and paresthesia, acquired in the setting of HIcV infection. (2) NP refractory to a least two previous analgesics	(1) Average score of 5 or higher on the pain intensity subscale.
Karst, et al. 2003 [57]	Presentation and examination consistent with hyperalgesia and allodynia. Diagnoses included: • NP of the left arm and right arm due to traumatic cervicobrachial plexus lesions • Neuropathic facial pain due to traumatic lesions of the left maxillary nerve, left trigeminal nerve, and mental nerve bilaterally. • NP behind the left ear due to traumatic lesion of the left great auricular nerve. • NP of the left forearm and hand due to traumatic lesion of the left radial nerve • NP in the left leg and right leg due to lumbar disk protrusion or intraspinal scar tissue after lumbar disk surgery • Pain in one or both legs due to traumatic spinal cord lesions • NP of the sole of the left foot due to compression of the tibial nerve (tarsal tunnel syndrome) • Neuropathic whole-body pain below the shoulders due to tethered cord syndrome after surgical removal of an intrathecal ependymoma • Neuropathic left facial pain (n = 1) of unknown cause.	(1) Stable levels of pain medications for at least 2 months, (2) Age 18 to 65 years, (3) Concomitant pain-relieving medications allowed were antipyretic and opioid analgesics, flupirtine, anticonvulsants, and antidepressants. (4) Pain for at least 6 months.

(continued)

Reference	Dx of NP	Inclusion criteria
Nurmikko, et al. 2007 [58]	(1) Unilateral peripheral NP and allodynia (2) Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination. (3) Patients with CRPS were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II)	(1) Age 18 or over, male or female (2) A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion (3) A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week (4) A stable medication regimen of analgesics for at least 2 weeks prior to study entry
Selvarajah, et al. 2010 [50]	Patients with chronic painful diabetic peripheral neuropathy (Neuropathy Total Symptom Score 6 [66] >4 and <16)	(1) At least 6 months of pain (2) Stable glycemic control (HbA1C <11%) (3) Those with persistent pain, despite an adequate trial of tricyclic antidepressants, were recruited.
Serpell, et al. 2013 [61]	(1) Had mechanical allodynia within the territory of the affected nerve(s) confirmed by either a positive response to stroking the allodynic area with a brush or to force applied by a monofilament. (2) At least one of the following underlying conditions, which caused their Peripheral NP: • post-herpetic neuralgia, • peripheral neuropathy, • focal nerve lesion, • radiculopathy or • CRPS type 2.	(1) Aged 18 or older, (2) At least a 6-month history of PNP and were receiving the appropriate treatment for their PNP. (3) Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) and pain that was not wholly relieved by their current therapy. (4) Analgesic regimen was stable for at least 2 weeks preceding study entry.
Svendsen, et al. 2004 [51]	(1) Diagnosis of multiple sclerosis (clinical definite multiple sclerosis and laboratory supported definite multiple sclerosis), (2) Assessed central pain after a clinical examination by a doctor. The criterion for central pain was: - pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside, - or quantitative sensory testing corresponding to at least one lesion in the central nervous system.	(1) Age between 18 and 55 years, (2) Central pain at the maximal pain site with a pain intensity score ≥3 on a 0-10 numerical rating scale. (3) We allowed concurrent spasm related pain if the patient was able to distinguish spasm related pain and central pain. (4) We allowed additional pain outside the maximal pain site if pain intensity was low and distinguishable from the central pain
Wade, et al. 2002 [60]	(1) Eligible patients had to have a neurological diagnosis and to be able to identify troublesome symptoms which were stable and unresponsive to standard treatments. (2) NP pain associated with muscle spasm and tremor and included multiple sclerosis (n=18), spinal cord injury (n = 4), brachial plexus damage (n=1), and limb amputation (n = 1)	
Wallace, et al. 2015 [52]	(1) Diabetes mellitus type 1 or type 2, who had stable glycemia (HbA1c ≤11%) and were maintained by diet or a stable regimen of diabetic therapy for at least 12 weeks before the evaluation. (2) Presence of both spontaneous and evoked pain in the feet, (3) At least a six-month history of painful diabetic peripheral neuropathy diagnosed according to research diagnostic criteria (using the Michigan Neuropathy Screening Instrument [69]), which included: - the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or electrophysiological abnormalities (distal leg sensory nerve conduction studies), - paresthesia and a pain of intensity of ≥ 4 on the 11-point NRS	(1) Participants were men and women. (2) Age 18 or older
Ware, et al. 2010 [62]	(1) NP of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia, (2) Average weekly pain intensity scores greater than 4 on a 10-cm visual analogue scale.	(1) Men and women aged 18 years or older. (2) Participants had a stable analgesic regimen and reported not having used cannabis during the year before the study. (3) normal liver function normal renal function, normal hematocrit and a negative result on human chorionic gonadotropin pregnancy test (if applicable).

(continued)

Reference	Dx of NP	Inclusion criteria
Wilsey, et al. 2008 [53]	(1) Patients with CRPS type I, spinal cord injury, peripheral neuropathy, or nerve injury. (2) The specific historic and physical findings included burning pain, skin sensitivity to light touching or cold, skin color changes, swelling, limited movement of the affected body part, motor neglect or abnormalities in skin temperature, hair growth, nail growth, and/or sweating.	(1) Previous cannabis exposure was required of all participants. (2) Refrain from smoking cannabis or taking oral synthetic delta-9-THC medications for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to confirm this provision.
Wilsey, et al. 2013 [54]	NP disorder: (1) CRPS type I, formerly known as reflex sympathetic dystrophy. (2) thalamic pain, (3) spinal cord injury, (4) peripheral neuropathy, (5) radiculopathy, or (6) nerve injury	(1) Required to refrain from smoking cannabis or taking oral synthetic THC medications for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to confirm this provision as much as was feasible. (2) Previous cannabis exposure (3) No depression.
Wilsey, et al. 2016b (exploratory) [55]	Individuals with injury and disease of the spinal cord	(1) Age >18 and <70 yrs. (2) Pain intensity >4 on a scale of 10
Wilsey, et al. 2016a (preliminary) [59]	NP as defined by Leeds Assessment of Neuropathic Symptoms and Signs [107]	(1) 18-70 yrs. (2) Pain intensity of 4/10.

Abbreviations: CRPS, complex regional pain syndrome; Dx, diagnosis; HbA1C, glycated hemoglobin; HIV-DSPN, human immunodeficiency virus associated distal sensory predominant polyneuropathy HIV-SN, human immunodeficiency virus associated sensory neuropathy, hr, hour; NP, neuropathic pain; NRS, numeral rating scale; PNP, peripheral neuropathic pain; THC, tetrahydrocannabinol; VAS, visual analog scale; yrs, years.

  - One study used a novel hand-held, battery-operated inhaler with software control to accurately control different doses of pharmacologically active granulated pharmaceutical-grade 22% THC (0.5 mg or 1.0 mg) [47].
  - One trial studied 2.5% to 9.4% THC concentrations administered via inhalation using a titanium pipe [62].
  - Four studies used inhaled vaporized cannabis as the treatment comparison [52,54,55,59] with THC concentrations ranging from 1% to 7%.
- CBDV: One study used 8 mL (400 mg) doses of CBDV dissolved in sesame oil taken orally [48].
- Synthetic cannabinoid: Two of the studies used capsules (synthetic cannabinoid analog CT-3 in 10 mg capsules [57] and synthetic THC molecule dronabinol in 2.5 mg capsules [51]).

5) Co-interventions

Due to the nature of NP conditions and the use of medications to relieve the pain burden by those experiencing it, patients continued taking medications in an attempt to reduce pain. All included studies, except three [49,51,59], required stable use of concomitant medications without adequate relief for a period of time leading up to the study and throughout the study. Two studies specifically excluded patient receiving medications including levodopa, sildenafil, and fentanyl [49], and those with the use of concomitant tricyclic anti-depressants, anticholinergics, antihistamines, and CNS depressants [51]. One study did not state any co-interventions [59]. One study [47] reported the use of concomitant medications for pain management, including anticonvulsants, benzodiazepines, antidepressants, analgesics, and anti-inflammatory drugs. Another trial [48] reported that the use of concomitant analgesics (including antidepressants and anticonvulsants) was allowed throughout the study. Participants in each study were asked not to use any non-study cannabinoid medication during the course of their study.

6) Outcomes

The primary outcomes of the included studies were NP intensity and spontaneous pain intensity at baseline and post-treatment, or baseline NP pain and reduction from baseline at post-treatment.

Table 4. Summary of Risk of bias for eligible studies

Study	Random Seq. Generation	Allocation Concealment	Blinding participants/ personnel	Blinding assessors/statistician	Incomplete Outcome Data	Selective Reporting	Other potential bias	Overall Bias
Abrams, et al. 2007 [63]	-	-	?	?	-	-	?	?
Almog, 2020 [47]	-	-	?	-	-	-	+	+
Berman, et al. 2004 [49]	-	-	?	?	-	-	+	+
Eibach, et al. 2020 [48]	-	-	?	?	?	-	?	?
Ellis, et al. 2009 [56]	-	-	+	-	-	-	?	+
Karst, et al. 2003 [57]	-	-	-	?	-	-	+	+
Nurmikko, et al. 2007 [58]	-	-	-	+	-	-	+	+
Selvarajah, et al. 2010 [50]	?	-	?	?	-	-	?	?
Serpell, et al. 2013 [61]	-	-	-	?	+	-	+	+
Svendsen, et al. 2004 [51]	-	-	?	-	-	-	?	?
Wade, et al. 2002 [60]	-	-	-	?	?	-	+	+
Wallace, et al. 2015 [52]	-	-	?	-	-	-	?	?
Ware, et al. 2010 [62]	-	?	?	?	-	-	?	?
Wilsey, et al. 2008 [53]	-	-	?	?	-	-	?	?
Wilsey, et al. 2013 [54]	-	-	?	?	?	-	?	?
Wilsey, et al. 2016b (exploratory) [55]	-	-	?	-	-	-	?	?
Wilsey, et al. 2016a (preliminary) [59]	?	+	+	+	?	-	?	+

KEY: + High risk of bias; - Low risk of bias; ? Unclear risk of bias

Secondary outcomes for reported pain included percentage improvement in NP intensity [70], responders with a 30% or more reduction in pain intensity, responders with a 50% or more reduction in pain intensity, brief pain inventory [71], pain disability index [72], painDETECT [73], McGill Pain Questionnaire [74], and Douleur Neuropathique 4 interview (DN4i) [40].

The included RCTs also reported quality of life outcomes: SF-36 [75], brief symptom inventory (BSI) [76], general health questionnaire (GHQ-12 or GHQ－28) [77], patient global impression change (PGIC) [78], and Euro quality of life (EQ-5D) [79]. For cognitive decline assessment, studies reported the Cambridge Neuropsychological Test Automated Battery (CANTAB) [80], trail-making test [81], and the short orientation-memory-concentration test [82]. Sleep quality was assessed using several recording methods, such as the insomnia severity index (ISI) [83], sleep disturbances, sleep disruption, and Leeds sleep evaluation questionnaire 65, and the box score 11 point scale (BS-11) [84]. Other secondary outcomes included expanded disability status (EDSS) [85], profile of mood states (PMOS) [86], and qualitative testing (allodynia, cold/hot threshold). Other outcomes reported included rescue medications, medication quantification scale [87], and adverse events [48] using common terminology criteria for adverse events version 4.03 (CTCTAE) [88].

3. Risk of bias in included studies

The trials included in this review were analyzed for the presence of risk of bias, including but not limited to allocation concealment, random sequence generation, blinding of investigators and participants, selective reporting, incomplete outcome data, and other potential sources of bias. Overall, the risk of bias was unclear in nine of the 17 RCTs (52.9%) [48,50–55,62,63], and a high risk of bias was found in eight of the 17 RCTs (47.1%) [47,49,56–61] (Tables 4 and 5; Fig. 2).

4. Adverse events

Adverse events (AEs) and side effects for the RCTs [47,49,62,63,51–54,56,58,60,61] included but were not limited to anxiety, sedation, dizziness, nausea, and fatigue. Two publications [55,59] reported that there were no serious side effects related to the study. One study [48] reported that thirty-one patients, (91.2%) had at least one study related AE, stating that diarrhea and dry mouth of mild severity were the most common AEs, and one

Table 5. Analysis of risk of bias for included studies

RISK OF BIAS	SUMMARY
Random sequence generation	Random sequence generation methods were found to be low risk of bias in fifteen studies as a computerized random generator [48,49,51,56–58,61,63] random number permutations [52], Latin square design [62], William's square [47,60], and web-based number generator [53–55] were used. An unclear risk of bias was identified in two of the studies as they stated the goal was randomization but the strategy for randomization was not specifically stated [50,59].
Allocation concealment	Allocation concealment was identified as low risk in fifteen trials. The interventions were prepared and packaged by a third party in identical packaging in seven [47,50,52,57,60,61,63], key study assignments were withheld in one 56, sealed envelopes were used in four [48,49,51,58] and the allocation was kept concealed in the pharmacy in three [53–55] trials. The risk of bias was unclear in two studies. One paper 62 stated "We have shown the feasibility of a single-dose delivery method for smoked cannabis, and that blinding participants to treatment allocation is possible using this method", but does not describe how. High risk of bias was given to one trial [59] for having no description of allocation concealment.
Blinding of participants/personnel	Blinding of participants and personnel was identified as low risk in four studies [57,58,60,61]. Placebo capsules were identical and randomization, labeling, and packaging in high-density polyethylene bottles and dispensed under blinded conditions in one study [57]. Study spray medication and placebo were taste- and color-matched with peppermint oil and coloring in three studies [58,60,61]. An unclear risk assessment was assigned to eleven studies [47,48,63,49–55,62]. Although there were identical pre-rolled cigarettes in one study, participants were required to have previous experience smoking cannabis63. Seven studies did not give enough information to determine level of blinding [47–50,53,55,62]. In one study although medication and placebo were in identical containers 67% of participants correctly identified active medication [51]. Similarly 89% of the subjects correctly identified the active medication in another study [54]. One study was assigned unclear risk of bias because of psychoactive effects of both placebo and treatment [52]. A high risk of bias for participants and personnel was assigned to two trials [56,59]. In one study all but one participant correctly identified the active treatment [56]. One study was assigned a high risk of bias because no blinding description was given [59].
Blinding assessors/statistician	Blinding of assessors and statisticians was identified as low risk in five studies with the key for study assignment withheld from investigation until analysis was completed [47,51,52,55,56]. Blinding of assessors and statisticians was assigned unclear risk bias for ten studies as they stated the trial was "double-blinded" but gave no description of blinding methods for assessors and/or statisticians [48–50,53,54,57,60–63]. Two studies were identified as high risk of bias for assessors and statisticians [58,59]. In one study the sponsor of the study participated in the analysis [58]. Another study did not indicate that blinding of assessors and/or statisticians was performed [59].
Incomplete outcome data	Twelve of the studies were assigned low riskof bias for incomplete outcome data; these studies had no missing outcome data reported [47,49,62,63,50–53,55–58]. Fourof the studies were identified as unclear risk of bias due to incomplete outcome data reporting [54,59,60]. Two studies lacked information on intent-to-treat analysis adherence [59,60]. One study had participants who were not included in the analysis, although reasons for non-inclusion were stated [54]. One study had patients drop out during the study that were not excluded from analysis and no information was given on point of study during which they withdrew [48]. One study was identified as high risk of bias of incomplete outcome data reported due to a withdrawal rate of 29.7% for the study [61].
Selective reporting	A low risk of bias was assigned to all studies [47,48,57–63,49–56] because all outcomes were described and presented as pre-specified.
Other potential sources of bias	An unclear risk of bias was assigned to eleven [48,50,63,51–56,59,62] studies. Nine had co-interventions (patients used concomitant medications for pain) [48,50,52–56,62,63] One studydid not state the co-interventions [59] and one trial [51] was funded by the drug company that manufactures the intervention, however the statistical analyses were blinded. A high risk of bias was identified in six studies [47,49,57,58,60,61] as the authors received funding by the intervention manufacturer with a proprietary interest in the medications used.
Overall bias	Overall, the risk of bias was unclear in nine of the seventeen RCTs (52.9%) [48,50–55,62,63], and a high risk of bias was found in eight of the seventeen RCTs (47.1%) [47,49,56–61].

Abbreviations: RCT, randomized controlled trial.

patient withdrew due to an AE (cough) during CBDV treatment. Another RCT [57] reported side effects of the trial in a subsequent paper [46]. One study [50] did not list the adverse events but stated that, of the 30 patients randomized, six withdrew because of adverse events.

5. Meta-analyses

1) THC/CBD

Five studies [49,50,58,60,61] reported a change in pain

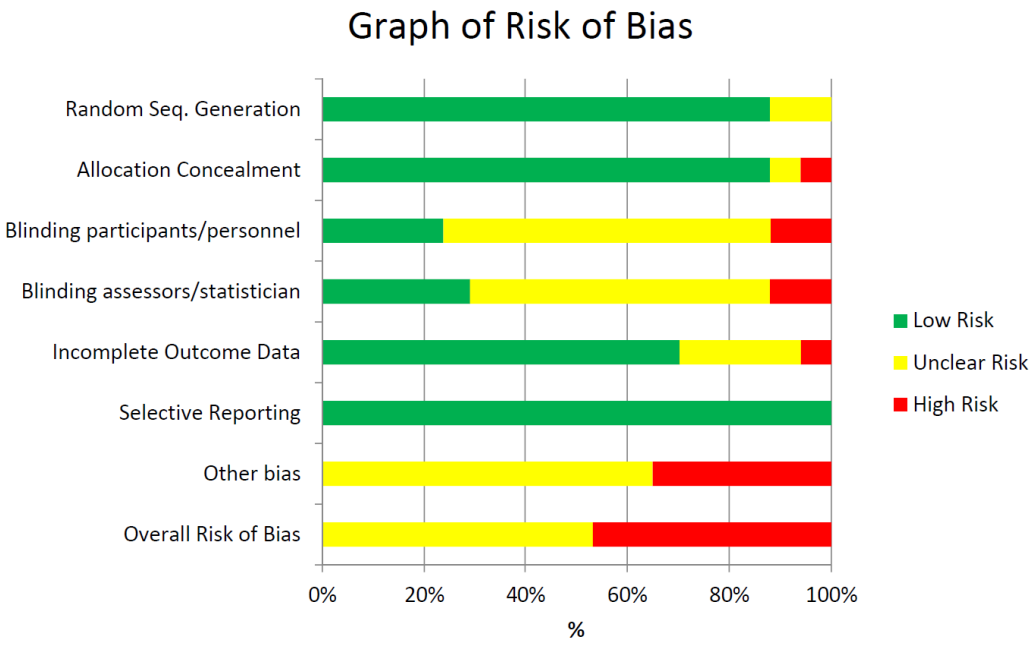


Fig. 2. Summary of risk of bias of eligible randomized controlled trials.

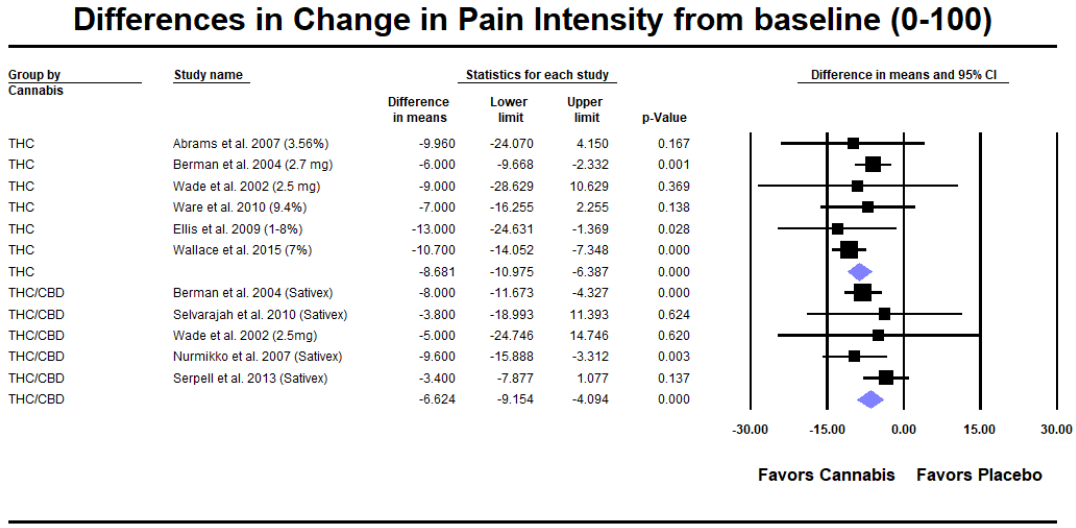
intensity (VAS or NRS 0-100) from baseline. Overall, THC/CBD significantly improved pain intensity by -6.6 units compared to placebo on a 0–100 scale (P < .001; Fig. 3a). Two studies [58,61] reported the number of patients with a 30% reduction in pain intensity. Patients who used THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain compared to patients receiving placebo (P = .008; Fig. 4a). Patients receiving THC/CBD intervention were 1.422 times more likely to achieve a 50% reduction in pain, although the difference was not statistically significant [58] (P = .37; Fig. 4b). There were no significant differences in the change in pain disability index (0-70) from baseline with THC/CBD compared to placebo in two studies [49,58] (P = .06; Fig. 5a), nor in the change in Brief Pain Inventory (BPI) pain intensity score [61](P = .29) and BPI pain interference score (P = .184).

Two studies [49,50] reported the McGill Pain Questionnaire (MPQ) post-treatment data. There were no statistical differences between THC/CBD and placebo in post-treatment MPQ VAS pain (P = .92; Fig. 5b), MPQ total score [49] (P = .08), present pain intensity (P = .19), sensory scale(P = .46), or affective scale (P = .67) [50]. Finally, this study reported changes in quality of life using the SF-36 questionnaire [50]. There were no statistically significant differences in any of the SF-36 subscales between the THC/CBD and placebo interventions (P = .37; Fig. 6a).

2) THC

Six studies [49,52,56,60,62,63] reported a change in pain intensity (VAS or NRS 0–100) from baseline. Overall, THC at varying dosages (1% to 9.4%) significantly improved pain intensity by -8.7 units on a 0–100 scale (P < .001; Fig. 3a). Two studies [52,63] reported a difference in the percent reduction in pain intensity from the baseline. Patients receiving THC had a -21% significantly higher improvement in pain intensity from baseline than patients in the placebo group (P = 0.005; Fig. 3c). Five studies [47,52,54–56,63] reported the number of patients with a 30% reduction in pain intensity. Patients receiving THC were 1.855 times more likely to achieve a 30% reduction in pain than patients in the placebo group (P < .001; Fig. 4a). One study [49] reported a change in the Pain Disability Index (0-70) from baseline. Overall, THC did not significantly improve the pain disability index on a 0–70 scale compared to placebo (P = .82; Fig. 5a).

A



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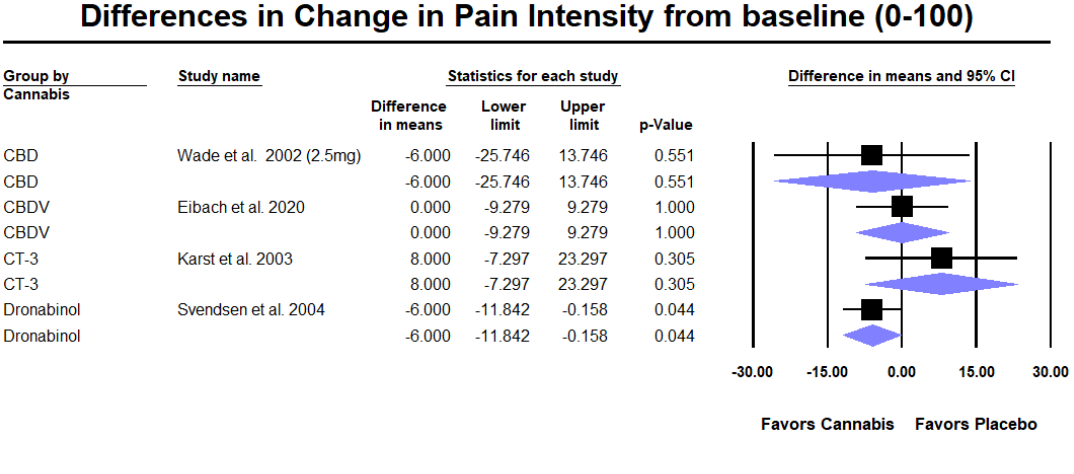

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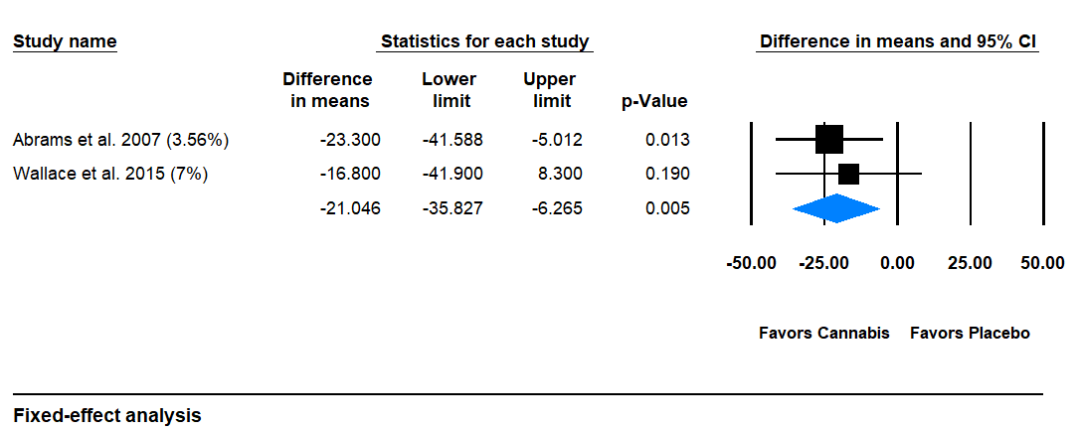

Fig. 3. Results of meta-analysis comparing cannabis to placebo intervention for neuropathic pain patients. Subgroup analyses for differences of change in pain intensity from baseline for (a) THC and THC/CBD studies and (b) CBD and synthetic cannabis interventions; (c) Percent reduction in pain intensity with THC. A $p \leq 0.05$ denotes a statistically significant difference. CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol.

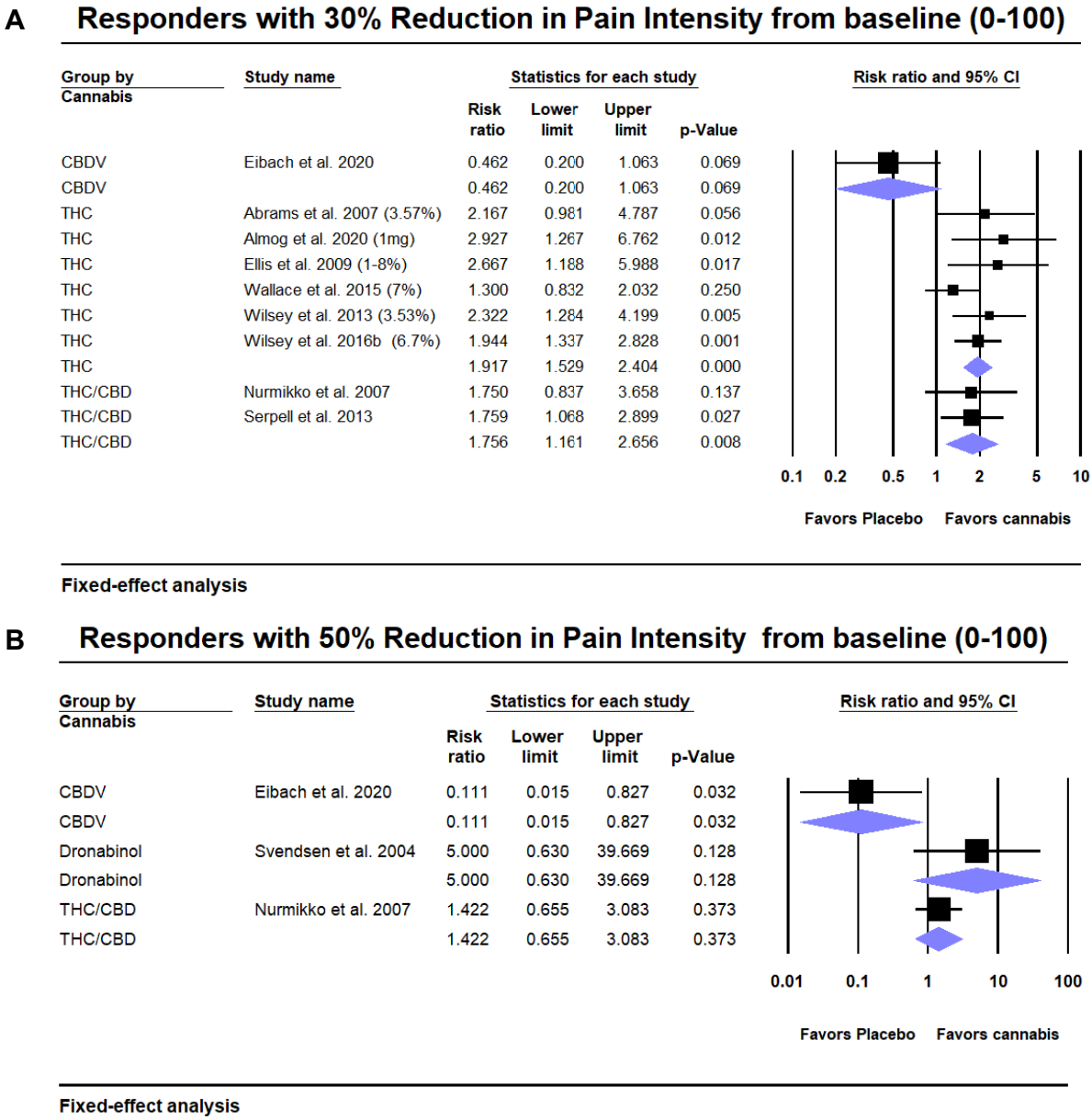

Fig. 4. Subgroup analyses for differences in number of responders with (a) 30% reduction and (b) 50% reduction in pain intensity from baseline (score 0-100). CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol.

Overall, THC significantly improved post-treatment MPQ VAS pain [49] (P = .02; Fig. 5b) and total score [49,62] (P = .03). One study [62] reported a non-significant improvement in post-treatment MPQ present pain intensity (P = .40), sensory scale (P = .59), and affective scale (P = .60).

3) CBD and CBDV

CBD: Overall, CBD [60] slightly improved pain intensity by -6.0 units on a 0–100 scale from baseline, and the difference was not significant with placebo (P = .55; Fig. 3b).

CBDV: One study [48] reported no difference in VAS pain intensity between the CBDV and placebo groups (P = 1.00; Fig. 3b). Patients who used CBDV were 53.8% less likely to achieve a 30% reduction in pain (P = .07; Fig. 4a) and 88.9% less likely to achieve a 50% reduction in pain compared to patients receiving placebo (P = .03;

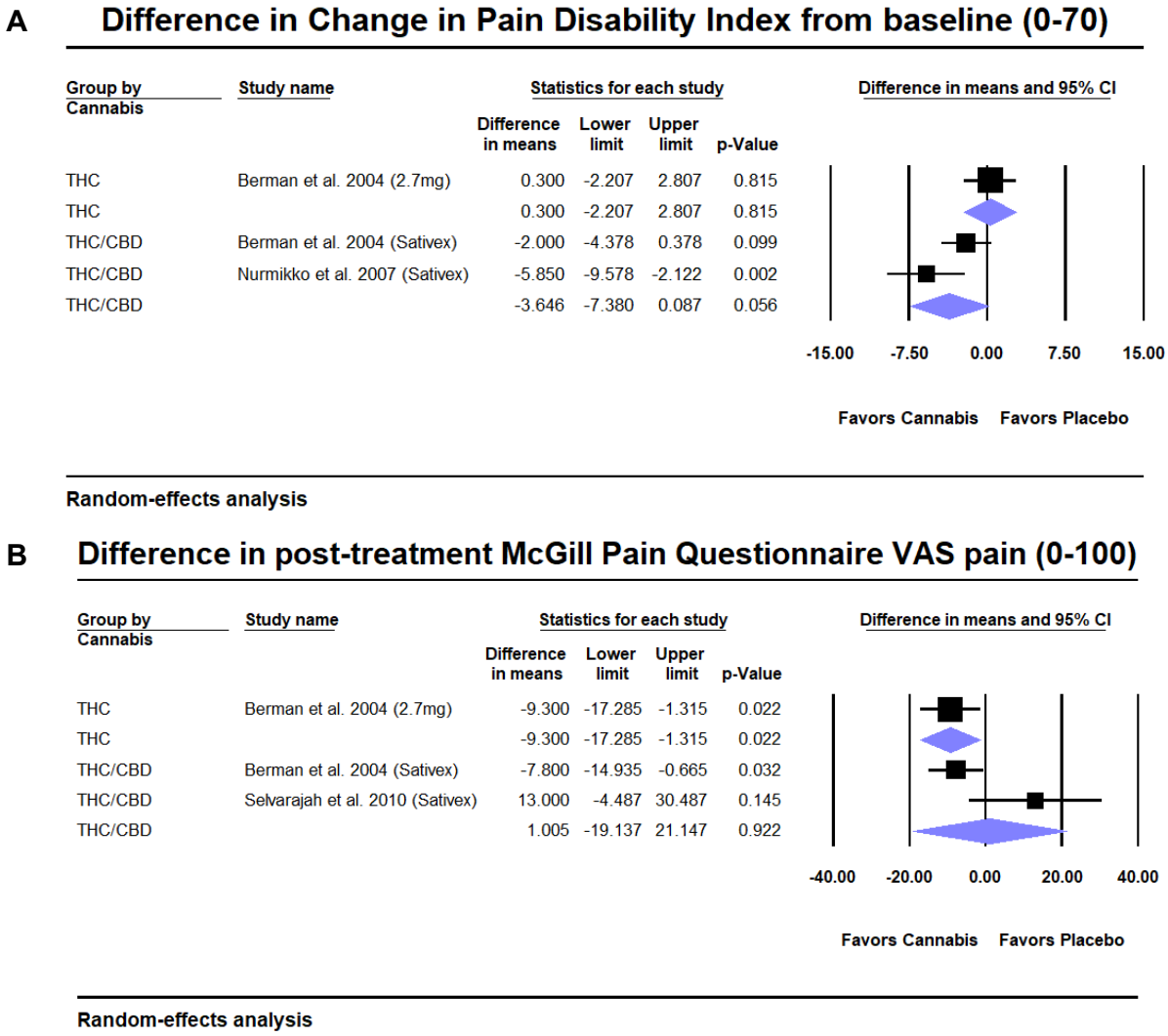

Fig. 5. Subgroup analyses for (a) differences of change in Pain Disability Index from baseline on a 0-70 scale; (b) differences in post-treatment McGill Pain Questionnaire Visual Analog Scale score on a 0-100 scale. CBD, cannabidiol; CBDV, cannabidivarin; CI, confidence interval; THC, tetrahydrocannabinol; VAS, visual analog scale.

Fig. 4b). There were no significant differences in BPI pain intensity score (P=.65) or BPI pain interference score between the CBDV and placebo groups (P = .36).

4) Synthetic cannabis

CT-3: One study [57] reported a change in pain intensity (0–100) from the baseline. There were no significant differences in the change in pain intensity between the CT-3 and placebo groups (P = .31; Fig. 3b).

Dronabinol: In one study [51], 2.5 mg capsules of dronabinol significantly improved pain intensity by -6.0 units on a 0–100 scale compared to placebo (P = .04; Fig. 3b). Patients receiving dronabinol were 5 times more likely to achieve a 50% reduction in pain than patients in the placebo group; however, this was not statistically significant (P = .13; Fig. 4b). There was a significant improvement in SF-36 reported mental health scores (P < .001), physical functioning (P < .001), and social functioning (P = .04) in the dronabinol group than in the placebo group (Fig. 6b).

6. Quality of the Evidence (GRADE)

1) THC/CBD

The quality of the evidence was moderate for THC/CBD interventions for the outcomes of change in

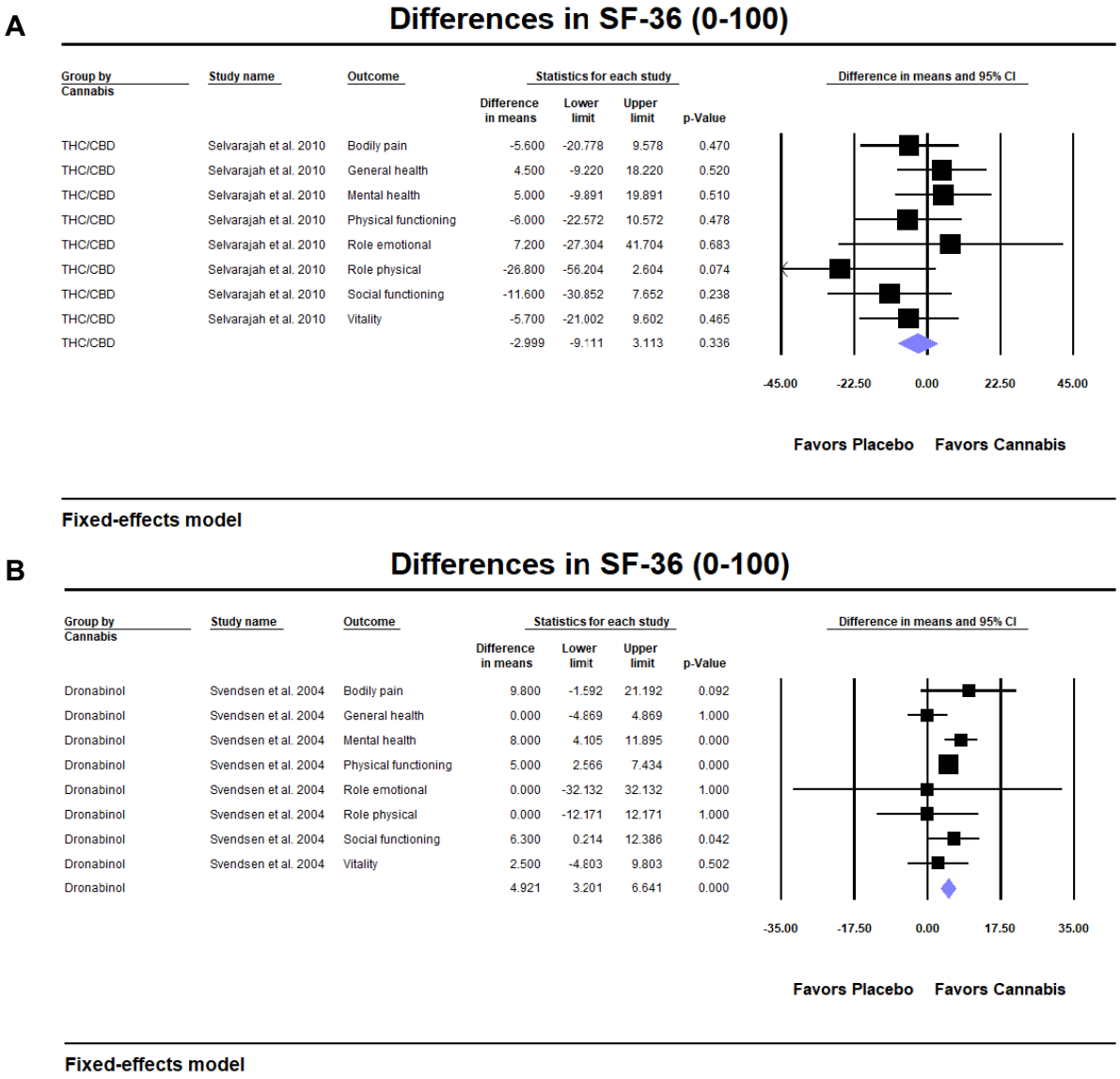

Fig. 6. Subgroup analyses for differences in post-treatment SF-36 subscales with (a) THC/CBD and (b) dronabinol. Higher SF-36 scores represent favorable quality of life. CBD, cannabidiol; CI, confidence interval; SF-36, 36 item short form survey; THC, tetrahydrocannabinol.

pain intensity from baseline (0–100) due to the unclear/high risk of bias of the studies pooled in the subgroup analyses. The quality of the evidence was low for the number of responders with a 30% reduction in pain and the change in pain disability index (Table 6) due to (a) the unclear/high risk of bias of the studies pooled in the subgroup analyses, (b) small sample size of participants in each analysis (<400), and (c) the small number of studies pooled (only two).

2) THC

Due to unclear or high risk of bias in the studies pooled in the subgroup analyses, the quality of the evidence was moderate for THC interventions for the outcomes of change in pain intensity from baseline (0–100) and number of responders with a 30% reduction in pain. The quality of the evidence was low for difference in percent reduction of pain intensity and MPQ total score (Table 6) due to the unclear/high risk of bias, small total sample size, and the small number of studies pooled (only two).

3) Other cannabis interventions

Only one study reported outcomes for dronabinol, CBD, CBDV, and CT-3; further studies are needed to

Table 6. Quality of the Evidence (GRADE [45]) for THC/CBD and THC interventions.

THC/CBD Interventions compared to Placebo for Neuropathic pain					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with THC/CBD (95% CI)
Change in pain intensity from baseline Scale from: 0 to 100.	522 (5studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias			The mean change in pain intensity from baseline in the intervention groups was -6.624 lower (-9.154to-4.094lower)
Responders with 30% reduction in pain intensity	359 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision	RR 1.756 (1.161to2.656)	157 per 1000	119 more per 1000 (from25moreto260more)
Change in pain disability index Scalefrom:0to70.	219 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean change in pain disability index in the intervention groups was 3.646 lower (7.380lowerto0.087higher)
McGill pain questionnaire VAS pain Scalefrom:0to100.	71 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean McGill pain questionnaire VAS pain in the intervention groups was 1.005 higher (19.137lowerto21.147higher)
THC interventions compared to Placebo for Neuropathic Pain					
Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95%CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with THC (95% CI)
Change in pain intensity from baseline Scalefrom:0to100.	332 (7studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias			The mean change in pain intensity from baseline in the cannabis groups was -8.681 lower (-10.975to-6.387lower)
Difference in percent reduction of pain intensity	87 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean difference in percent reduction of pain intensity in the cannabis groups was –21.046 lower (-35.827to-6.265lower)
Responders with 30% reduction in pain intensity	353 (6studies)	⊕⊕⊕⊖ MODERATE[1] duetoriskofbias	RR 1.917 (1.529to2.404)	309 per 1000	283 more per 1000 (from163moreto434more)
McGill pain questionnaire - Total score Scalefrom:0to45.	137 (2studies)	⊕⊕⊖⊖ LOW[1,2] duetoriskofbias,imprecision			The mean McGill pain questionnaire - total score in the intervention groups was 2.197 lower (4.219to0.176lower)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

[1]All studies at unclear or high risk of bias
[2]Only two studies, wide confidenc eintervals, small sample size

Abbreviations: CBD, cannabidiol; CI, confidence interval; GRADE, grading of recommendations assessment, development and evaluation; RR, Risk ratio; THC, tetrahydrocannabinol; VAS, visual analog scale.

confirm our results, and the quality of the evidence was very low.

DISCUSSION

1. Main findings

This systematic review included 17 studies involving 861 adult participants. Each of the included studies compared cannabis-based medications with placebo controls. The studies varied in methods of delivery,

concentration, and dosage of cannabis-based medications and included both plant-based and synthetic cannabinoids. Subgroup analyses were undertaken to provide overall estimates for THC, THC/CBD, CBD, CBDV, and synthetic cannabinoid medications (CT-3 and dronabinol) used as interventions. A significant reduction in NP intensity from baseline was observed in studies of THC and THC/CBD with moderate quality of evidence (Table 6); however, the decrease in VAS pain was not clinically significant (-6 units for THC/CBD and -9 units for THC on a 0–100 scale). Participants in two studies with THC/CBD were 1.756 times more likely to achieve a 30% reduction in pain (low quality evidence) and 1.422 times more likely to achieve a 50% reduction in pain in one study (very low evidence). Those receiving THC were 1.917 times more likely to achieve a 30% reduction in pain (moderate-quality evidence) compared to placebo. Due to the unclear/high risk of bias of the included studies, small sample sizes, and wide confidence intervals, the quality of the evidence was moderate to low. Low to moderate quality of evidence indicated inconclusive results that THC and THC/CBD may be efficacious in reducing chronic NP.

Only one study reported a change in VAS pain from baseline for dronabinol, CBD, CBDV, and CT-3; further studies are needed to confirm our results. Dronabinol showed a significant decrease in pain of -6 units compared to placebo in one study, as well as significant improvements in quality of life measured with the SF-36. CBD, CBDV, and CT-3 did not show a significant reduction from baseline pain compared to placebo in the included studies.

The most common AEs and side effects were anxiety, sedation, dizziness, nausea, and fatigue. Two publications [55,59] reported that there were no studies related to serious side effects. One study [48] reported that 91.2% of the patients had at least one study related AE, stating that diarrhea and dry mouth of mild severity were the most common AEs, and one patient withdrew due to an AE (cough) during CBDV treatment. One study [50] stated that, of the 30 patients randomized, six withdrew because of adverse events.

2. Agreements and disagreements with other studies or reviews

Several reviews [89–91] share optimistic conclusions that the use of cannabis-based medications is moderately effective, tolerable, and safe in the treatment of patients with NP. In a qualitative systematic review of cannabis-based medications for non-cancer pain [89], which included 11 RCTs on chronic NP, the authors reported that cannabis-based medications were “modestly” effective in the treatment of NP, and that it was “reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain.” Several of the included trials also demonstrated a significant improvement in sleep without serious adverse events, which were generally described as well tolerated, short lived, or mild-to-moderate [89].

In a review of the effectiveness of cannabinoids in the management of chronic nonmalignant NP [90], the authors concluded that cannabinoids provided significant pain reduction in both the short and long term, and that cannabinoids should be considered as an effective add-on, if not an alternative therapy, for the treatment of chronic NP. Their review also suggested that cannabis-based therapies may provide effective analgesia in chronic NP conditions that are refractory to other interventions, and that cannabinoids also improve nausea, sleep quality, anxiety, and appetite. Adverse events were described as minor in nature [90].

In an individual patient data meta-analysis of inhaled cannabis for the treatment of chronic NP [91], data from 178 participants in five RCTs provided evidence that inhaled cannabis resulted in short-term reductions in chronic NP for every five to six patients treated (NNTB = 5.6, CI = 3.4 to 14) for a more than 30% reduction in pain scores compared to placebo. From their data, they inferred that this effect applies to chronic painful neuropathies of different etiologies. They also reported that withdrawals due to adverse events were rare. Other

clinical guidelines and systematic reviews consider cannabis-based medications as third-or fourth-line therapy for chronic NP if the already accepted therapies (tricyclic antidepressants (TCAs), anticonvulsants) have failed to achieve effective results [92,93].

On the other hand, there are also reviews [21,94,95] that do not support cannabis-based medications for the treatment of NP. The Neuropathic Pain Special Interest Group (NeuPSIG) conducted a systematic review of randomized double-blind studies of oral and topical pharmacotherapy for NP [94]. The authors identified nine trials of Sativex (an oromucosally applied spray containing 27 mg/ml of THC and 25 mg/ml of cannabidiol) in NP. Only two of these studies were found to be favorable, leading to a weak recommendation against their use in NP. Abuse, negative results, diversion, potential misuse, and long-term mental health risks in susceptible individuals were all reasons for their recommendation against the use of Sativex in NP.

In a systematic review of cannabis-based medications for chronic NP in adults [21], the authors analyzed eight studies with 1,001 participants. A total of 20.9% of participants in the cannabis-based medications and 17.3% in the placebo group reported pain relief of 50% or greater (NNTB = 20). According to their predefined categories, there were no clinically relevant benefits of cannabis-based medications. Cannabis-based medications were superior to placebo in the reduction of mean pain intensity (P =.008). According to Cohen's categories, there was a small effect size, indicating minimal clinically important improvement. Finally, 39.4% of participants in the cannabis-based medications and 32.7% of participants in the placebo group reported pain relief of 30% or greater (NNTB = 11). The quality of evidence was determined to be moderate to low due to indirectness, imprecision, and inconsistency. They concluded that there is "no high-quality evidence for the efficacy of any cannabis-based medicine (herbal cannabis, plant-derived THC (dronabinol), synthetic THC (nabilone), and plant-derived THC/CBD combinations) in any condition with chronic NP". Mücke et al. [21] stated that they performed a quantitative analysis, which included unpublished studies with negative results, while the authors of the studies with more favorable outcomes did not include the data of studies that are only available in databases; they also excluded studies with a very short duration. In addition, the same authors found that using cannabis-based medications for chronic NP showed moderate-quality evidence that more participants dropped out due to AEs with cannabis-based medications compared to placebo, and low-quality evidence that more participants reported any AEs and AEs of the central nervous system and psychiatric disorders with all cannabis-based medications pooled together than with placebo. This was also in accordance with another systematic review [96] that analyzed eight trials of cannabis-based medicine in chronic NP.

Another systematic review and meta-analysis that examined cannabis treatment for chronic pain [95] concluded that the current evidence might suggest that treatment of chronic pain with cannabinoid compounds may pose a greater risk than benefit to the patient because of the possible appearance of the pain as a secondary problem in the subject.

3. Overall completeness and applicability of evidence

Parallel RCTs or crossover placebo-controlled studies were identified from electronic databases including MEDLINE, Web of Science, EMBASE, and the Cochrane library limited to English language up to 2/1/2021. Cannabis-based medications included THC, THC/CBD, CBD, CBDV, CT-3, and dronabinol. The results of this systematic review apply to patients with chronic NP between ages 18–77. The trials were conducted in the USA, UK, Europe, and Israel, and may not reflect or apply to other countries.

These results are applicable to NP conditions including central NP (MS, brachial plexus avulsion), complex regional pain syndrome (CRPS) type II, HIV-related neuropathy, painful diabetic neuropathy, peripheral polyneuropathies of other etiologies, phantom limb pain, postherpetic neuralgia, postoperative or traumatic

peripheral nerve lesions, spinal cord injuries, nerve plexus injuries, and trigeminal neuralgia (TN).

The applicability of the evidence to routine care is limited because some of the included studies excluded individuals with current or past alcohol and/or substance abuse, significant medical issues (cardiovascular disease, poorly controlled hypertension, active epilepsy), significant psychiatric illnesses, and those naïve to cannabis-derived products.

The reliability of the combined results is limited because of the small sample size, short duration, different types of interventions, routes of administration, doses and dose schedules, and the different types of NPs.

4. Heterogeneity of the review

This systematic review included only RCTs comparing cannabis-based medications with a placebo. There was heterogeneity in terms of the intervention (THC/CBD, CBD, CBDV, synthetic cannabis), for which the review authors conducted subgroup analyses. Review authors conducted subgroup analyses with similarly reported outcomes. Different types of cannabis were utilized in the included studies, with varied mechanisms of action, routes of administration, dosages, and schedule. The route of administration of cannabis varied from smoked, inhaled, vaping, spray, and oil. The minimum and maximum doses of THC were 1% and 9.4%, respectively. NP types varied from HIV distal sensory predominant polyneuropathy, CRPS II, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, focal nerve lesion, radiculopathy, multiple sclerosis, injury and disease of the spinal cord, nerve plexus injury, and postoperative or traumatic peripheral nerve lesions due to trauma. The diagnosis of NP was based on clinical symptoms and various tools depending on the diagnosis (see Results section).

5. Implications for research

This systematic review and meta-analyses demonstrated low to moderate quality of evidence due to high or unclear risk of bias, small number of studies, and limited duration. The quality of the evidence was low to moderate because of the unclear blinding of samples. Some studies received funding from drug companies, while others had co-interventions. However, a few studies have not completely reported the outcome data. In conclusion, a high overall risk of bias was assigned to six studies, and an unclear overall risk of bias was assigned to eight studies. The meta-analyses highlight the need for future high-quality double-blinded randomized, placebo-controlled studies receiving cannabis-based medications with intent-to-treat analyses and full reporting of outcome data as stated in published protocols without biases.

The present systematic review has several limitations that will be valuable for future studies. These limitations included the variability in the length of the studies evaluated, the short trial durations, small sample sizes, variability of route of administration, multiple doses, concomitant therapies, and lack of knowledge of possible drug-drug interactions or long-term effects.

The Committee for Medicinal Products for Human Use (CHMP) published guidelines on clinical medicinal products intended for the treatment of neuropathic pain [97]. These guidelines require that the study duration for chronic NP trials be at least 12 weeks after a stable dose is achieved to exclude a transient effect. Due to the increasing number of drugs approved for NP, they also recommend that a three-arm study (study drug – comparator–placebo) should be undertaken to assess the comparative efficacy and safety of a new product. Long-term clinical trials may also help to determine whether the effect of cannabis on chronic NP is sustainable.

The optimal dose and ratio of THC/CBD need to be determined for different types of NPs. Determining the optimal dose, treatment duration, and individual titrations would allow for a better balance between beneficial and adverse effects, especially in older vulnerable and young populations [98,99].

Medicinal cannabis is controversial and remains illegal and is unavailable in many states in the United States.

There may also be a long-lasting stigma associated with smoking cannabis [100]. Some individuals may prefer not to take cannabis-based medications if the route of administration is inhaled due to social stigmas or if long-term adverse effects of smoked cannabis outweigh the benefits [99,101-104]. Determining the most beneficial route of administration and type of cannabinoid with these factors in mind would allow individuals with an interest in medicinal cannabis to select or decline this treatment option, especially if the reduction in pain intensity is modest. There may also be differences in efficacy, adverse effects, or abuse potential among the different types of cannabinoids and routes of administration.

The use of cannabis for other medical conditions should also be investigated in high-quality randomized placebo-controlled clinical trials. Clinical evidence will help with appropriate prescribing, prevent misuse and harm, and possibly reduce the use of opioids and their associated risks [105,106].

One study [63] in this review required that participants have experience using cannabis-containing products, while another excluded patients with prior experience [54]. Future studies should include individuals who have not used cannabis-based medications and those that used them to study the efficacy, safety, and tolerability of all types of patients. Future studies should also explore other cannabis-based agents that may be useful in reducing pain, such as CT-3.

The types of NP varied greatly in this systematic review with meta-analysis due to a lack of RCTs on cannabis-based medications in the treatment of any specific type of NP. Future research on the efficacy of cannabis-based medications should focus on the specific causes of NP because the mechanisms are different.

6. Implications for clinical practice

Currently, therapeutic options for the treatment of NP often provide inadequate relief. A review of the current research indicates that, although there is moderate and low-quality evidence to support significant changes in pain intensity from baseline in NP with the use of some forms of THC, THC/CBD, and the synthetic cannabinoid dronabinol, there is currently no high-quality evidence for the efficacy of any form of cannabis-based medication for the treatment of NP. Clinical research to determine the efficacy of cannabinoid medications in the treatment of NP is confounded by the variable etiologies of NP as well as factors such as varying doses, routes of administration, concurrent medications of NP patients, potential adverse effects, and lack of uniform testing across studies. This makes statistical analysis to determine the efficacy difficult and clinical recommendations for its use tenuous. Additional long-term studies with more uniform study parameters are needed to achieve more clinically relevant recommendations. Potential adverse events often related to psychoactive effects may limit the clinical use of cannabis-based medications for some patients. A high degree of variability among study participants warrants caution with its use as a potential therapeutic option for patients with NP.

In conclusion, THC/CBD and THC interventions provided statistically significant improvements in pain intensity in NP patients and were more likely to provide a 30% reduction of NP when smoked or vaped at different concentrations (3.56% to 9.4% THC) or using a spray (THC 2.5-2.7 mg & CBD 2.5 mg per 100mL) compared to placebo. The evidence for THC/CBD and THC was moderate to low quality. Therefore, Further studies are needed for CBD, CBDV, and the synthetic cannabinoids dronabinol and CT-3, as only one study reported outcomes on these cannabis-based interventions compared to placebo.

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REFERENCES

1. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain 2011; 152: 2204-5.
2. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers 2017; 3: 17002.
3. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008; 136: 380-7.
4. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. J Pain Res 2016; 9: 457-67.
5. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 2009; 32: 1-32.
6. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009; 10: 895-926.
7. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. P T 2017; 42: 180-8.
8. Kalant OJ. Report of the indian hemp drugs commission, 1893-94: a critical review. Int J Addict 1972; 7: 77-96.
9. America. Public Law 113 – 79 113th Congress An Act 2014; 1-357.
10. McPartland JM. Cannabis systematics at the levels of family, genus, and species. Cannabis Cannabinoid Res 2018; 3: 203-12.
11. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag 2001; 6: 80-91.
12. Cherney JH, Small E. Industrial hemp in North America: production, politics and potential. Agronomy 2016; 6: 58.
13. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006; 58: 389-462.
14. Owens B. Drug development: the treasure chest. Nature 2015; 525: S6-8.
15. Hillard CJ, Weinlander KM, Stuhr KL. Contributions of endocannabinoid signaling to psychiatric disorders in humans: genetic and biochemical evidence. Neuroscience 2012; 204: 207-29.
16. Hill MN, Patel S, Campolongo P, Tasker JG, Wotjak CT, Bains JS. Functional interactions between stress and the endocannabinoid system: From synaptic signaling to behavioral output. J Neurosci 2010; 30: 14980-6.
17. Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. Annu Rev Med 2006; 57: 553-74.
18. Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? Prog Lipid Res 2011; 50: 193-211.
19. Klein TW, Cabral GA. Cannabinoid-induced immune

suppression and modulation of antigen-presenting cells. J Neuroimmune Pharmacol 2006; 1: 50-64.
20. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor H. Dronabinol and chronic pain: importance of mechanistic considerations. Expert Opin Pharmacother 2014; 15: 1525-34.
21. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018; 7; 3: CD012182
22. Maldonado R, Baños JE, Cabañero D. The endocannabinoid system and neuropathic pain. Pain 2016; 157: S23-32.
23. Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci 2007; 10: 870-9.
24. Fine PG, Rosenfeld MJ. Cannabinoids for Neuropathic Pain. Curr Pain Headache Rep 2014; 18: 451.
25. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets 2009; 8: 403-21.
26. Hohmann AG, Herkenham M. Localization of cannabinoid CB(1) receptor mRNA in neuronal subpopulations of rat striatum: a double-label in situ hybridization study. Synapse 2000; 37: 71-80.
27. Herkenham M. Characterization and localization of cannabinoid receptors in brain: an in vitro technique using slide-mounted tissue sections. NIDA Res Monogr 1991; 112: 129-45.
28. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. Life Sci 1995; 56: 2103-9.
29. Tsou K, Brown S, Sañudo-Peña MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 1998; 83: 393-411.
30. Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 1999; 11: 4213-25.
31. Siegling A, Hofmann HA, Denzer D, Mauler F, De Vry J. Cannabinoid CB1 receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol 2001; 415: R5-7.
32. Lim G, Sung B, Ji RR, Mao J. Upregulation of spinal cannabinoid-1-receptors following nerve injury enhances the effects of Win 55,212-2 on neuropathic pain behaviors in rats. Pain 2003; 105: 275-83.
33. Zhang J, Hoffert C, Vu HK, Groblewski T, Ahmad S, O'Donnell D. Induction of CB2 receptor expression in the rat spinal cord of neuropathic but not inflammatory chronic pain models. Eur J Neurosci 2003; 17: 2750-4.
34. Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr Pain Headache Rep 2015; 19: 50.
35. Boyaji S, Merkow J, Elman RNM, Kaye AD, Yong RJ, Urman RD. The Role of Cannabidiol (CBD) in Chronic Pain Management: An Assessment of Current Evidence. Curr Pain Headache Rep 2020; 24: 4.
36. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. BMJ 2014; 348: f7656.
37. Binder A, Baron R. The pharmacological therapy of chronic neuropathic pain. Dtsch Arztebl Int 2016; 113: 616-25.
38. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999; 83: 389-400.
39. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. J Pain 2004; 5: 143-9.
40. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005; 114: 29-36.
41. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 21; 6: e1000097.
42. Higgins J, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011.
43. Cochran WG. The combination of estimates from different

experiments. Biometrics 1954; 10: 101-29.

44. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
45. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64: 383-94.
46. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology 2005; 48: 1164-71.
47. Almog S, Aharon-Peretz J, Vulfsons S, Ogintz M, Abalia H, Lupo T, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: a randomized, double-blinded, placebo-controlled trial. Eur J Pain 2020; 24: 1505-16.
48. Eibach L, Scheffel S, Cardebring M, Lettau M, Özgür Celik M, Morguet A, et al. Cannabidivarin for HIV-associated neuropathic pain: a randomized, blinded, controlled clinical trial. Clin Pharmacol Ther 2021; 109: 1055-62.
49. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004; 112: 299-306.
50. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care 2010; 33: 128-30.
51. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004; 329: 253.
52. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain 2015; 16: 616-27.
53. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9: 506-21.
54. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013; 14: 136-48.
55. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain 2016; 17: 982-1000.
56. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009; 34: 672-80.
57. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA 2003; 290: 1757-62.
58. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007; 133: 210-20.
59. Wilsey BL, Deutsch R, Samara E, Marcotte TD, Barnes AJ, Huestis MA, et al. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. J Pain Res 2016; 9: 587-98.
60. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003; 17: 21-9.
61. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain 2014 18: 999-1012.
62. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010; 182: E694-701.
63. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68: 515-21.

64. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008; 70: 1630-5.
65. Parrott AC, Hindmarch I. The leeds sleep evaluation questionnaire in psychopharmacological investigations-a review. Psychopharmacology (Berl) 1980; 71: 173-9.
66. Bastyr EJ 3rd, Price KL, Bril V; MBBQ Study Group. Development and validity testing of the neuropathy total symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. Clin Ther 2005; 27: 1278-94.
67. Harden NR, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "budapest criteria") for complex regional pain syndrome. Pain 2010; 150: 268-74.
68. Woldeamanuel YW, Kamerman PR, Veliotes DG, Phillips TJ, Asboe D, Boffito M, et al. Development, validation, and field-testing of an instrument for clinical assessment of HIV-associated neuropathy and neuropathic pain in resource-restricted and large population study settings. PLoS One 2016; 11: e0164994.
69. Moghtaderi A, Bakhshipour A, Rashidi H. Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. Clin Neurol Neurosurg. 2006; 108: 477-81.
70. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the neuropathic pain scale. Neurology 1997; 48: 332-8.
71. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singap 1994; 23: 129-38.
72. Pollard CA. Preliminary validity study of the pain disability index. Percept Mot Skills 1984; 59: 974.
73. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006; 22: 1911-20.
74. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1: 277-99.
75. Jenkinson, C., Coulter, A., Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993; 306(Sf 36): 1437-40.
76. Derogatis LR, Melisaratos N. The brief symptom inventory: an introductort report. Psychol Med 1983; 13: 595-605.
77. Goldberg DP, Hillier VF. A scaled version of the general health questionnaire. Psychol Med 1979; 9: 139-45.
78. Perrot S, Lantéri-Minet M. Patients' global impression of change in the management of peripheral neuropathic pain: clinical relevance and correlations in daily practice. Eur J Pain 2019; 23: 1117-28.
79. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199-208.
80. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimers Dement 2008; 4: 428-37.
81. O'Donnell WE, Reynolds DM, De Soto CB. Neuropsychological impairment scale (NIS): initial validation study using trailmaking test (A & B) and WAIS digit symbol (scaled score) in a mixed grouping of psychiatric, neurological, and normal patients. J Clin Psychol 1983; 39: 746-9.
82. Wade DT, Vergis E. The short orientation-memory-concentration test: a study of its reliability and validity. Clin Rehabil 1999; 13: 164-70.
83. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med 2001; 2: 297-307.
84. Jensen MP, Miller L, Fisher LD. Assessment of pain during medical procedures: A comparison of three scales. Clin J Pain 1998; 14: 343-9.
85. Kurtzke JF. A new scale for evaluating disability in multiple sclerosis. Neurology 1955; 5: 580-3.
86. Nyenhuis DL, Yamamoto C, Lucheta T, Terrien A, Parmentier A. Adult and geriatric normative data and validation of the profile of mood states. J Clin Psychol 1999; 55: 79-86.
87. Harden RN, Weinland SR, Remble TA, Houle TT, Colio S, Steedman S, et al. Medication Quantification Scale version III: update in medication classes and revised detriment weights by survey of American Pain Society

physicians. J Pain 2005; 6: 364-71.

88. Common Terminology Criteria for Adverse events. US Dept of Health and Human Services, National Institutes of Health, National Cancer Institute. 2009;version 4
89. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015; 10: 293-301.
90. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache 2015; 29: 7-14.
91. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain 2015; 16: 1221-32.
92. Petzke F, Enax-Krumova EK, Haeuser W. Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain. a systematic review of randomized controlled studies. Schmerz 2016; 30: 62-88.
93. Mu A, Weinberg E, Moulin DE, Clarke H. Pharmacologic management of chronic neuropathic pain. Can Fam Physician 2017; 63: 844-52.
94. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14: 162- 73.
95. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009; 10: 1353-68.
96. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015; 313: 2456-73.
97. Committee for Medicinal Products for Human Use (CHMP). Guideline on Clinical Investigation of Medicinal Products for the Treatment of Neuropathic Pain. European Medicines Agency. Evaluation of Medicines for Human Use. Doc. Ref. CPMP/EWP/252/03 Rev. 1. 2007.
98. DuPont RL, Lieberman JA. Young brains on drugs. Science 2014; 344: 557.
99. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014; 370: 2219-27.
100. Bottorff JL, Bissell LJ, Balneaves LG, Oliffe JL, Capler NR, Buxton J. Perceptions of cannabis as a stigmatized medicine: A qualitative descriptive study. Harm Reduct J 2013; 10: 2.
101. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol 2014; 113: 187-90.
102. Preuss UW, Watzke AB, Zimmermann J, Wong JW, Schmidt CO. Cannabis withdrawal severity and short-term course among cannabis-dependent adolescent and young adult inpatients. Drug Alcohol Depend 2010; 106: 133-41.
103. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. Alcohol 2005; 35: 265-75.
104. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. Curr Opin Pulm Med 2014; 20: 173-9.
105. Wendelboe AM, Mathew R, Chongsuwat T, Rainwater E, Wendelboe MA, Wickersham E, et al. Is there less opioid abuse in states where marijuana has been decriminalized,either for medicinal or recreational use? A Clin-IQ. J Patient-Centered Res Rev 2019; 6: 267-73.
106. Hayes MJ, Brown MS. Legalization of medical marijuana and incidence of opioid mortality. JAMA Intern Med 2014; 174: 1673-4.
107. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. Pain 2001; 92: 147-57.